Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1626GMS

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * *	* *	* *	* *	* Welcome to STN International * * * * * * * * * *
NEWS	1			Web Page for STN Seminar Schedule - N. America
NEWS	2	AUG	06	CAS REGISTRY enhanced with new experimental property tags
NEWS	3	AUG	06	FSTA enhanced with new thesaurus edition
NEWS	4	AUG	13	CA/CAplus enhanced with additional kind codes for granted patents
NEWS	5	AUG	20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS	6	AUG	27	Full-text patent databases enhanced with predefined
				patent family display formats from INPADOCDB
NEWS	7	AUG	27	USPATOLD now available on STN
NEWS	8	AUG	28	CAS REGISTRY enhanced with additional experimental
				spectral property data
NEWS	9	SEP	07	STN AnaVist, Version 2.0, now available with Derwent
				World Patents Index
NEWS	10		13	
NEWS			13	
NEWS	12	SEP	17	
				1967-1998
NEWS	13	SEP	17	CAplus coverage extended to include traditional medicine
				patents
NEWS				EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS	15	OCT		CA/CAplus enhanced with pre-1907 records from Chemisches Zentralblatt
NEWS		OCT		BEILSTEIN updated with new compounds
NEWS	17	NOV		Derwent Indian patent publication number format enhanced
NEWS		NOV		WPIX enhanced with XML display format
NEWS		NOV		ICSD reloaded with enhancements
NEWS		DEC		LINPADOCDB now available on STN
NEWS		DEC		BEILSTEIN pricing structure to change
NEWS				USPATOLD added to additional database clusters
NEWS		DEC		IMSDRUGCONF removed from database clusters and STN
NEWS		DEC		DGENE now includes more than 10 million sequences
NEWS	25	DEC	17	TOXCENTER enhanced with 2008 MeSH vocabulary in MEDLINE segment
NEWS	26	DEC	17	MEDLINE and LMEDLINE updated with 2008 MeSH vocabulary
NEWS	27	DEC	17	
NEWS	28	DEC	17	STN Viewer enhanced with full-text patent content
				from USPATOLD
NEWS	29	JAN	02	STN pricing information for 2008 now available

NEWS EXPRESS 19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2,

CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),

04/18/2008 Page 1

AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

NEWS HOURS STN Operating Hours Plus Help Desk Availability

NEWS LOGIN Welcome Banner and News Items

NEWS IPC8 For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

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FILE 'HOME' ENTERED AT 13:56:08 ON 07 JAN 2008

=>

Uploading
THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Do you want to switch to the Registry File?

Choice (Y/n):

Switching to the Registry File...

Some commands only work in certain files. For example, the EXPAND command can only be used to look at the index in a file which has an index. Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of commands which can be used in this file.

=> FILE REGISTRY

COST IN U.S. DOLLARS

SINCE FILE TOTAL ENTRY SESSION 0.21 0.21

FULL ESTIMATED COST

FILE 'REGISTRY' ENTERED AT 13:56:20 ON 07 JAN 2008 USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT. PLEASE SEE "HELP USAGETERMS" FOR DETAILS. COPYRIGHT (C) 2008 American Chemical Society (ACS)

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STRUCTURE FILE UPDATES: 6 JAN 2008 HIGHEST RN 960045-19-6
DICTIONARY FILE UPDATES: 6 JAN 2008 HIGHEST RN 960045-19-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information

on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=>

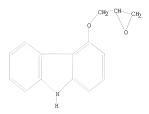
Uploading C:\Program Files\Stnexp\Queries\10553957.str

```
chain nodes :
14 15 19
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 16 17 18
chain bonds :
5-19 11-14 14-15 15-16
ring bonds :
1-2 1-6 2-3 3-4 4-7 5-6 5-9 6-7 7-10 8-9 8-13 9-10 10-11 11-12 12-13
16-17 16-18 17-18
exact/norm bonds :
5-6 5-9 11-14 16-17 16-18 17-18
exact bonds :
5-19 7-10 14-15 15-16
normalized bonds :
1-2 1-6 2-3 3-4 4-7 6-7 8-9 8-13 9-10 10-11 11-12 12-13
isolated ring systems :
containing 1:
```

Match level: 1:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:Atom 17:Atom 18:Atom 19:CLASS

L1 STRUCTURE UPLOADED

=> d l1 L1 HAS NO ANSWERS L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s 11

SAMPLE SEARCH INITIATED 13:56:34 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 5 TO ITERATE

100.0% PROCESSED 5 ITERATIONS 0 ANSWERS SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**

PROJECTED ITERATIONS: STO 234

PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=> s l1 sss full

FULL SCREEN SEARCH COMPLETED - 73 TO ITERATE

100.0% PROCESSED 73 ITERATIONS 14 ANSWERS SEARCH TIME: 00.00.01

L3 14 SEA SSS FUL L1

=> FIL HCAPLUS

COST IN U.S. DOLLARS SINCE FILE TOTAL ENTRY SESSION

FULL ESTIMATED COST 178.36 178.57

FILE 'HCAPLUS' ENTERED AT 13:56:46 ON 07 JAN 2008
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04/18/2008 Page 4

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FILE COVERS 1907 - 7 Jan 2008 VOL 148 ISS 2 FILE LAST UPDATED: 6 Jan 2008 (20080106/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s 13 L4 48 L3

=> FIL REGISTRY COST IN U.S. DOLLARS

FULL ESTIMATED COST

SINCE FILE TOTAL ENTRY SESSION 18.83 197.40

FILE 'REGISTRY' ENTERED AT 14:01:10 ON 07 JAN 2008 USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT. PLEASE SEE "HELP USAGETERMS" FOR DETAILS. COPYRIGHT (C) 2008 American Chemical Society (ACS)

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STRUCTURE FILE UPDATES: 6 JAN 2008 HIGHEST RN 960045-19-6
DICTIONARY FILE UPDATES: 6 JAN 2008 HIGHEST RN 960045-19-6

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TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to

http://www.cas.org/support/stngen/stndoc/properties.html

=>

Uploading C:\Program Files\Stnexp\Queries\10553957a.str

```
14 15 16 17 18 26 27 28 29 30 31 32
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 20 21 22 23 24 25
chain bonds :
5-18 11-14 14-15 15-16 16-17 16-30 17-29 21-31 22-26 26-27 27-28 28-29
31 - 32
ring bonds :
1-2 1-6 2-3 3-4 4-7 5-6 5-9 6-7 7-10 8-9 8-13 9-10 10-11 11-12 12-13
20-21 20-25 21-22 22-23 23-24 24-25
exact/norm bonds :
5-6 5-9 11-14 16-30 21-31 22-26
exact bonds :
5-18 7-10 14-15 15-16 16-17 17-29 26-27 27-28 28-29 31-32
normalized bonds :
1-2 1-6 2-3 3-4 4-7 6-7 8-9 8-13 9-10 10-11 11-12 12-13 20-21 20-25
21-22 22-23 23-24 24-25
isolated ring systems :
containing 1 : 20 :
```

Match level :

chain nodes :

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom 12:Atom 13:Atom 14:CLASS 15:CLASS 16:Atom 17:Atom 18:CLASS 20:CLASS 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom 26:CLASS 27:CLASS 28:CLASS 29:CLASS 30:CLASS 31:CLASS 32:CLASS

L5 STRUCTURE UPLOADED

=> d 15 L5 HAS NO ANSWERS L5 STR

Structure attributes must be viewed using STN Express query preparation.

=> s 15

SAMPLE SEARCH INITIATED 14:01:31 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 8 TO ITERATE

100.0% PROCESSED

8 ITERATIONS

4 ANSWERS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
PROJECTED ITERATIONS: BATCH **COMPLETE**
PROJECTED ANSWERS: 4 TO 200

T. C

4 SEA SSS SAM L5

=> s 15 sss full

FULL SEARCH INITIATED 14:01:37 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 301 TO ITERATE

100.0% PROCESSED 301 ITERATIONS

95 ANSWERS

SEARCH TIME: 00.00.01

L7

95 SEA SSS FUL L5

Uploading C:\Program Files\Stnexp\Queries\10553957b.str

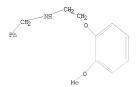
chain nodes:
1 8 9 10 11 12 13 14
ring nodes:
2 3 4 5 6 7
chain bonds:
1-11 1-14 3-12 4-8 8-9 9-10 10-11 12-13
ring bonds:
2-3 2-7 3-4 4-5 5-6 6-7
exact/norm bonds:
3-12 4-8
exact bonds:
1-11 1-14 8-9 9-10 10-11 12-13
normalized bonds:
2-3 2-7 3-4 4-5 5-6 6-7

Match level :

1:Atom 2:CLASS 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:CLASS 9:CLASS 10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS

L8 STRUCTURE UPLOADED

=> d 18 L8 HAS NO ANSWERS L8 STR



Structure attributes must be viewed using STN Express query preparation.

=> s 18

SAMPLE SEARCH INITIATED 14:04:09 FILE 'REGISTRY' SAMPLE SCREEN SEARCH COMPLETED - 686 TO ITERATE

100.0% PROCESSED 686 ITERATIONS 1 ANSWERS

15 ANSWERS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE** BATCH **COMPLETE**

PROJECTED ITERATIONS: 12149 TO 15291 PROJECTED ANSWERS:

1 TO

1 SEA SSS SAM L8

=> s 18 sss full

FULL SEARCH INITIATED 14:04:15 FILE 'REGISTRY' FULL SCREEN SEARCH COMPLETED - 13036 TO ITERATE

100.0% PROCESSED 13036 ITERATIONS

SEARCH TIME: 00.00.01

L10 15 SEA SSS FUL L8

=> FIL HCAPLUS

SINCE FILE TOTAL ENTRY SESSION COST IN U.S. DOLLARS FULL ESTIMATED COST 358.10 555.50

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=> d his

(FILE 'HOME' ENTERED AT 13:56:08 ON 07 JAN 2008)

```
FILE 'REGISTRY' ENTERED AT 13:56:20 ON 07 JAN 2008
               STRUCTURE UPLOADED
L2
              0 S L1
             14 S L1 SSS FULL
     FILE 'HCAPLUS' ENTERED AT 13:56:46 ON 07 JAN 2008
L4
             48 S L3
    FILE 'REGISTRY' ENTERED AT 14:01:10 ON 07 JAN 2008
               STRUCTURE UPLOADED
L6
              4 S L5
             95 S L5 SSS FULL
L7
L8
               STRUCTURE UPLOADED
L9
              1 S L8
L10
             15 S L8 SSS FULL
     FILE 'HCAPLUS' ENTERED AT 14:04:20 ON 07 JAN 2008
=> s 17
L11
         1715 L7
=> s 110
L12
           28 L10
\Rightarrow s 14 and 112
            9 L4 AND L12
=> s 113 and catalyst
        786783 CATALYST
        783681 CATALYSTS
       1006285 CATALYST
                 (CATALYST OR CATALYSTS)
L14
             3 L13 AND CATALYST
=> s 114 and znc12
         38620 ZNCL2
L15
             1 L14 AND ZNCL2
=> s 111 and process
       2546449 PROCESS
       1733561 PROCESSES
       3795605 PROCESS
                 (PROCESS OR PROCESSES)
1.16
           116 L11 AND PROCESS
=> s 116 and 14
           14 L16 AND L4
L17
=> s 116 and 112
L18
           6 L16 AND L12
=> s 117 and catalyst
        786783 CATALYST
        783681 CATALYSTS
       1006285 CATALYST
                 (CATALYST OR CATALYSTS)
1.19
             2 L17 AND CATALYST
```

```
=> s 118 and catalvst
        786783 CATALYST
        783681 CATALYSTS
       1006285 CATALYST
                 (CATALYST OR CATALYSTS)
L20
             2 L18 AND CATALYST
=> d his
     (FILE 'HOME' ENTERED AT 13:56:08 ON 07 JAN 2008)
     FILE 'REGISTRY' ENTERED AT 13:56:20 ON 07 JAN 2008
               STRUCTURE UPLOADED
              0 S L1
L3
             14 S L1 SSS FULL
     FILE 'HCAPLUS' ENTERED AT 13:56:46 ON 07 JAN 2008
             48 S L3
L4
    FILE 'REGISTRY' ENTERED AT 14:01:10 ON 07 JAN 2008
L5
                STRUCTURE UPLOADED
L6
              4 S L5
             95 S L5 SSS FULL
1.8
               STRUCTURE UPLOADED
L9
              1 S L8
L10
             15 S L8 SSS FULL
    FILE 'HCAPLUS' ENTERED AT 14:04:20 ON 07 JAN 2008
L11
          1715 S L7
L12
            28 S L10
L13
              9 S L4 AND L12
L14
              3 S L13 AND CATALYST
L15
             1 S L14 AND ZNCL2
L16
           116 S L11 AND PROCESS
L17
            14 S L16 AND L4
L18
             6 S L16 AND L12
L19
             2 S L17 AND CATALYST
             2 S L18 AND CATALYST
L20
=> d 13 ibib abs hitstr tot
YOU HAVE REQUESTED DATA FROM FILE 'REGISTRY' - CONTINUE? (Y) /N:end
=> d 113 ibib abs hitstr tot
L13 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:
                         2005:1260624 HCAPLUS
DOCUMENT NUMBER:
                         144:22806
TITLE:
                         Process for the preparation of carvedilol
INVENTOR(S):
                         Kankan, Rajendra Narayanrao; Rao, Dharmaraj
                         Ramachandra
PATENT ASSIGNEE(S):
                         Cipla Limited, India; Wain, Christopher Paul
SOURCE:
                         PCT Int. Appl., 29 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:
                         Patent
LANGUAGE:
                         English
```

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	TENT										ICAT					ATE	
	2005																
	W:	AE,	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,
		GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KM,	KP,	KR,	KZ,
		LC,	LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NA,
		NG.	NI,	NO.	NZ,	OM,	PG,	PH,	PL,	PT.	RO,	RU,	SC.	SD,	SE,	SG,	SK,
		SL,	SM,	SY,	TJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,
			ZM,														
	RW:	BW.	GH,	GM,	KE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,
		AZ,	BY,	KG,	KZ,	MD,	RU,	TJ,	TM,	AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,
		EE,	ES,	FI,	FR,	GB,	GR,	HU,	IE,	IS,	IT,	LT,	LU,	MC,	NL,	PL,	PT,
		RO.	SE.	SI,	SK,	TR.	BF,	BJ,	CF.	CG,	CI,	CM,	GA,	GN,	GO,	GW,	ML,
		MR.	NE.	SN.	TD.	TG											
ΑU	2005	2451	82		A1		2005	1201		AU 2	005-	2451	82		2	0050	519
CF	2566	197			A1		2005	1201		CA 2	005-	2566	197		2	0050	519
E	1756	057			A1		2007	0228		EP 2	005-	7441	87		2	0050	519
	R:	AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	IE,
		IS,	IT,	LI,	LT,	LU,	MC,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR		
JE	2007	5380	61		Т		2007	1227		JP 2	007-	5174	24		2	0050	519
11	2006	MN01	302		A		2007	0608		IN 2	006-	MN13	02		2	0061	107
PRIORIT	Y APP	LN.	INFO	. :						GB 2	004-	1127	3	- 1	A 2	0040	520
										WO 2	005-	GB19	78	1	W 2	0050	519
OTHER S	OURCE	(S):			CASI	REAC	Т 14	4:22	806								

AB A process for the preparation of carvedilol I (R = H) was disclosed and comprised aromatization/reduction of 1,2,3,9-tetrahydro-4H-carbazol-4-one by refluxing with Raney Ni and NaOH in water for 20 h to form 4-hydroxy-9H-carbazole, reaction of resulting alc. with epichlorohydrin using tetrabutylammonium bromide and NaOH in water to give 4-oxiranylmethoxy-9H-carbazole, reaction of the intermediate epoxide with M60-Z-06H00(CH2)ZNHCHZPh using K2CO3 in water to give carvedilol N-benzyl derivative I (R = CH2Ph), and finally, debenzylation of I (R = CH2Ph) using Pa/C in EtOAc and water to give the desired carvedilol. This invention further provided carvedilol prepared by the disclosed process, and pharmaceutical compns. containing the same, for therapeutic uses, such as adrenergic B-receptor antagonists, vasodilators and treatment of angina pectoris.

Ι

IT 3246-03-5
RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of carvedilol for use in pharmaceutical compns. as adrenergic B-receptor antagonists and vasodilators useful for the treatment of hypertension and angina pectoris)

RN 3246-03-5 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

51997-51-4P, 4-Oxiranylmethoxy-9H-carbazole

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of carvedilol for use in pharmaceutical compns. as adrenergic β-receptor antagonists and vasodilators useful for the treatment of hypertension and angina pectoris)

RN 51997-51-4 HCAPLUS

9H-Carbazole, 4-(2-oxiranvlmethoxv)- (CA INDEX NAME) CN

REFERENCE COUNT: THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:1128799 HCAPLUS

DOCUMENT NUMBER: 143:386916

TITLE: An improved process for the manufacture of carvedilol

Kankan, Rajendra Narayan Rao; Rao, Dharamraj

INVENTOR(S): Ramchandra Cipla Ltd., India PATENT ASSIGNEE(S):

SOURCE: Indian, 11 pp. CODEN: INXXAP

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE IN 186587 Α1 20011006 IN 1999-B0583 19990817

04/18/2008 Page 13 GI

PRIORITY APPLN. INFO.: OTHER SOURCE(S): IN 1999-B0583 CASREACT 143:386916; MARPAT 143:386916 19990817

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

- AB An improved process for the manufacture of Carvedilol I, a potent antihypertensive (no biol. data given) by catalytic hydrogenation of N-substituted Carvedilol II [RI = (un)substituted CH2Ph; formed by reacting carbazole III with a substituted amine IVI. Thus, N-alkylating benzylamine with 2-(2-methoxyphenoxy)ethyl bromide followed by reaction of the resulting N-[2-(2-methoxyphenoxy)ethyl)benzenemethanamine hydrochloride with 4-(2,3-epoxypropoxy)carbazole, and subsequent hydrogenation of the II [RI = Ch2Ph] afforded carvedilol I.
- CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]-, hydrochloride (9CI) (CA INDEX NAME)

HC1

- IT 3246-03-5 51997-51-4, 4-(2,3-Epoxypropoxy)carbazole
 RL: RCT (Reactant); RACT (Reactant or reagent)
 (improved process for the manufacture of carvedilol)
 RN 3246-03-5 HCAPLUS
- CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

- RN 51997-51-4 HCAPLUS
- CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

L13 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN ACCESSION NUMBER: 2004:1154673 HCAPLUS

English

DOCUMENT NUMBER: 142:93675

TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol

Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar INVENTOR(S):

Sun Pharmaceutical Industries Limited, India PATENT ASSIGNEE(S): SOURCE: PCT Int. Appl., 27 pp.

CODEN: PIXXD2 Patent

DOCUMENT TYPE: LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT				KIN	D	DATE				ICAT				D.	ATE	
WO 2004				A1	_	2004	1229			004-				2	0040	304
W:	AE,	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,
	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,
	GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KZ,	LC,
	LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NA,	NI,
	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,
	ТJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW
RW:	BW,	GH,	GM,	KΕ,	LS,	MW,	ΜZ,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	AZ,
	BY,	KG,	KZ,	MD,	RU,	TJ,	TM,	AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,
	ES,	FI,	FR,	GB,	GR,	HU,	ΙE,	IT,	LU,	MC,	NL,	PL,	PT,	RO,	SE,	SI,
	SK,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,	ΝE,	SN,
	TD,	TG														
IN 2003	MU00	647		A		2005	0211		IN 2	003-	MU64	7		2	0030	620
US 2006	2708	58		A1		2006	1130		US 2	005-	5539	57		2	0051	019
PRIORITY APP	LN.	INFO	. :						IN 2	003-	MU64	7		A 2	0030	620
									IN 2	003-	MU72	1		A 2	0030	717
									WO 2	004-	IN52			W 2	0040	304
OTHER SOURCE	(S):			CAS	REAC	T 14	2:93	675;	MAR	PAT	142:	9367	5			

^{*} STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

- AR The present invention provides a process for preparation of 1-[9H-carbazo1-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the
 - product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).
- 3246-03-5, N-[2-[2-(Methoxy)phenoxy]ethyl]benzylamine 51997-51-4, 4-(Oxiranylmethoxy)-9H-carbazole 95093-95-1,
 - (S)-4-(Oxiranylmethoxy)-9H-carbazole 95093-96-2,
 - (R)-4-(Oxiranvlmethoxy)-9H-carbazole RL: RCT (Reactant); RACT (Reactant or reagent)
- (reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)
- RN 3246-03-5 HCAPLUS
- Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME) CN

- RN 51997-51-4 HCAPLUS
- 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME) CN

RN 95093-95-1 HCAPLUS

CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.

RN 95093-96-2 HCAPLUS

CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

REFERENCE COUNT:

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:556143 HCAPLUS

DOCUMENT NUMBER: 137:125080

TITLE: Process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temperatures and

catalyst loading

INVENTOR(S): Scalone, Michelangelo; Zeibig, Thomas Albert

PATENT ASSIGNEE(S): Hoffmann-LaRoche Inc., Switz. SOURCE: U.S. Pat. Appl. Publ., 19 pp.

CODEN: USXXCO DOCUMENT TYPE: Patent.

LANGUAGE: English FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

		ENT :																ATE	
		2002						2002										0020	
	US	6777	559			B2		2004	0817										
		2434																	
	WO	2002	0590	89		A2		2002	0801		WO	2002	-EP	83			- 2	20020	122
	WO	2002	0590	89		A3		2002	1031										
		W:	ΑE,	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BE	3, B	, BI	, B	Υ,	BZ,	CA,	CH,	CN,
			CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC	, E	, E	, F	I,	GB,	GD,	GE,	GH,
			GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE	, KO	, KI	, K	R,	KZ,	LC,	LK,	LR,
			LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN	I, M	7, M	, M	Z,	NO,	NZ,	PH,	PL,
			PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SI	, T.	r, Ti	1, T	R,	TT,	TZ,	UA,	UG,
			UZ,	VN,	YU,	ZA,	zw												
		RW:	GH,	GM,	KE,	LS,	MW,	MZ,	SD,	SL,	SZ	, T	, U	, Z	М,	ZW,	ΑT,	BE,	CH,
			CY,	DE,	DK,	ES,	FI,	FR,	GB,	GR,	ΙE	, I	, LU	J, M	C,	NL,	PT,	SE,	TR,
			BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	GÇ), GI	7, MI	, M	R,	NE,	SN,	TD,	TG
		2002																	
	EP	1355	880			A2		2003	1029		EP	2003	-71	673			- 2	20020	122
		R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GF	ì, I:	, L	, L	U,	NL,	SE,	MC,	PT,
								RO,											
	JΡ	2004	5194	65		T		2004	0702		JΡ	2003	-559	391			- 2	20020	122
	IN	2003	CN01	126		A		2005	0422		IN	2003	-CN:	.126			2	20030	722
	MX	2003	PA06	606		A		2003	0922		MX	2000	-PA	606			2	20030	723
	US	2004	1277	23		A1		2004	0701		US	200	1-763	3296			- 2	20040	122
	US	7169	935			B2		2007	0130										
PRIOR	RITY	APP	LN.	INFO	. :													20010	
																		20020	
											WO	2003	-EP	83			W 2	20020	122

OTHER SOURCE(S):

CASREACT 137:125080; MARPAT 137:125080 AB A process for the preparation heterocyclic indene analogs, especially with the preparation

of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves

cyclocarbonylation followed by saponification This process avoids high temps. and

high catalyst loadings.

51997-51-4P, 4-Oxiranylmethoxy-9H-carbazole

RL: IMF (Industrial manufacture); PREP (Preparation)

(process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)

51997-51-4 HCAPLUS

9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

тт 3246-03-5

RL: RCT (Reactant); RACT (Reactant or reagent) (process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps, and catalyst loading)

3246-03-5 HCAPLUS RN

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethvl]- (CA INDEX NAME)

REFERENCE COUNT:

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:747162 HCAPLUS

DOCUMENT NUMBER: 135:288690

TITLE: Intermediates for preparing the R- or S- enantiomer and N-benzyl derivatives of 1-[9'H-carbazol-4'-yloxy]-

3-[2"-(2"'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol]

INVENTOR(S):

Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyoergyi Donath; Nemeth,

Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy,

Peter Kotay; Seres, Peter PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.

SOURCE: Eur. Pat. Appl., 9 pp.

CODEN: EPXXDW Patent

DOCUMENT TYPE: LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1142874	A2	20011010	EP 2001-111214	19981124
EP 1142874	A3	20031022		
R: BE, DE, ES,	FR, GB	, IT, SI, LT	, LV, RO	
HU 9802180	A1	20001228	HU 1998-2180	19981001

04/18/2008 Page 19

RU	2216	539			C2		2003	1120	RU	1	998-	1207	00		1	9981	118
RU	2245	875			C2		2005	0210	RU	2	003-	1077	72		1	9981	118
EP	9180	55			A1		1999	0526	EF	1	998-	1221	14		1	9981	124
EP	9180	55			B1		2003	0423									
EP	9180	55			B2		2006	0426									
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB, G	R,	IT,	LI,	LU,	NL,	SE,	MC,	PT,
		IE,	SI,	LT,	LV,	FI,	RO										
PRIORITY	APP	LN.	INFO	. :					HU	1	997-	2209		1	A 1	9971	124
									HU	1	998-	2180		1	A 1	9981	001
									EF	1	998-	1221	14	1	A3 1	9981	124
									RU	1	998-	1207	00	1	A 1	9981	118

OTHER SOURCE(S): CASREACT 135:288690

BB R-(+)-1-[N-benzyl-2'-[[2''-(methoxyphenoxy)ethyl]amino]-3-[9'''H-carbazol4'''-yloxy]propan-2-ol and S-(-)-1-[N-benzyl-2'-[[2''(methoxyphenoxy)ethyl]amino]-3-[9'''H-carbazol-4'''-yloxy]propan-2-ol and
the R- or S- enantiomer of carvedilol are prepared in high yield and
selectivity by the ring-opening cleavage of the resp. R- or S- enantiomer
of 4-(oxiranylmethoxy)-9H-carbazole with N-2-[(2'methoxyphenoxy)ethyl]benzylamine to give the N-benzyl derivs., and the
chiral carvedilol enantiomers are prepared by the reductive debenzylation of
the resp. chiral N-benzyl derivs. in the presence of Pd(C and hydrazine

hydrate. IT 95093-95-1, S-4-(Oxiranylmethoxy)-9H-carbazole 95093-96-2

, R-4-(Oxiranylmethoxy)-9H-carbazole

RL: RCT (Reactant); RACT (Reactant or reagent)

(intermediates for preparing the R- or S- enantiomer and N-benzyl derivs.
 of 1-[9'#-carbazol-4'-yloxy]-3-[2"-(2"'-methoxyphenoxy)ethylamino]propa
 n-2-ol [carvedilol])

RN 95093-95-1 HCAPLUS

CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.

RN 95093-96-2 HCAPLUS

CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

IT 3246-03-5P 120606-08-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediates for preparing the R- or S- enantiomer and N-benzyl derivs.
of 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'-methoxyphenoxy)ethylamino]propa
n-2-ol (carvedia(1))

RN 3246-03-5 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

RN 120606-08-8 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]-, hydrochloride (9CI) (CA INDEX NAME)

HC1

L13 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN ACCESSION NUMBER: 2001:747161 HCAPLUS

DOCUMENT NUMBER: 135:288689

TITLE: Process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2"-(2"'- methoxyphenoxy)ethylamino]-propan-2-ol

[carvedilol]
INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simiq, Gyula;

Gregor, Tamas; Vereczkey, Gyoergyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy, Peter Kotay; Seres, Peter
PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung.

SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW

KIND

DATE

DOCUMENT TYPE: Patent

LANGUAGE: English FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

EP 1142873 EP 1142873		20011010 20030910	EP 2001-111213	19981124
EP 1142873	B1	20040421		
R: BE, D	E, ES, FR, GE	B. IT. SI.	I.T. I.V. BO	
HU 9802180	A1	20001228		19981001
RU 2216539	C2	20031120		19981118
RU 2245875				19981118
EP 918055	A1		EP 1998-122114	19981124
EP 918055	B1	20030423		
EP 918055	B2	20060426		
R: AT, B	E. CH. DE. DK	(. ES. FR. (GB, GR, IT, LI, LU, N	L. SE. MC. PT.
	I, LT, LV, FI			-,,,
PRIORITY APPLN. IN		,	HU 1997-2209	A 19971124
1111011111 11111111 1111			HU 1998-2180	
			EP 1998-122114	
			RU 1998-120700	A 19981118
OTHER SOURCE(S):	CASREA	ACT 135:288	689	
AB A process for	preparing 1-	-[9'H-carba	zo1-4'-yloxy]-3-[{2'-	(2'-
met.hoxyphenoxy	v)ethvl}aminc	olpropan-2-	ol as well as acid ad	dition salts of this
			N-[2-(2'-methoxy-phe	
			ichlorohydrin, and th	
			ethyl}amino]-3-propan	
			resulting 1-N-benzyl-	
(mot how mhano	virathirlamina)	-3-10:11-00	rhagol-4!-ulovulnrona	n=2=n1 ic

APPLICATION NO.

DATE

(methoxyphenoxyethylamino) -3 - [9'H-carbazol-4'-yloxy]propan-2-ol is debenzylated by catalytic hydrogenation and, if desired, the $1-[9'H-carbazol-4'-yloxy]-3-[\{2'-(2'-methoxyphenoxy)ethyl)amino]propan-2-ol thus obtained is reacted with acids to yield acid addition their salts, or if desired, liberating the free <math>1-[9'H-carbazol-4'-yloxy]-3-\{[2]-(2'-methoxyphenoxy)ethyl]aminopropan-2-ol base from acid addition salts thereof and, if desired, converting the free <math>1-[9'H-carbazol-4'-yloxy]-3-\{2]-(2'-methoxyphenoxy)ethylamino-propan-2-ol base into other acid addition salts and/or, if desired, comparing the enantiomers.$

IT 3246-03-5P 120606-08-8P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2-(2'-yloxy]

methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])

RN 3246-03-5 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

RN 120606-08-8 HCAPLUS
CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]-, hydrochloride (9CI)
(CA INDEX NAME)

O-CH2-CH2-NH-CH2-Ph

HC1

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

L13 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN ACCESSION NUMBER: 1999:344783 HCAPLUS

DOCUMENT NUMBER: 130:352184

DOCUMENT NUMBER: 130:352184

TITLE: Preparation of carvedilol

INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula;
Gregor, Tamas; Vereczkey, Gyorgyi Donath; Nemeth,
Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor;
Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy,

Peter Kotay; Seres, Peter

PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung. SOURCE: Eur. Pat. Appl., 17 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

04/18/2008 Page 23

-																
									EP	1998-	1221:	14		19	9811	24
	P 9180															
E	P 9180)55			B2		2006	0426								
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB, G	R, IT,	LI,	LU,	NL, S	E, 1	MC,	PT,
		IE,	SI,	LT,	LV,	FI,	RO									
	U 9802								HU						9810	01
C	Z 2965	21			В6		2006	0412	CZ	1998-	3561			19	9811	04
C	Z 2974	145			B6		2006	1213	CZ	2004-	1111			19	9811	04
H	R 9805	590			B1		2003	1231	HR	1998-	590			19	9811	12
S	K 2841	109			B6				SK							
	U 2216								RU							
P	U 2245	875			C2		2005	0210	RU	2003-	1077	72		19	9811	18
E	P 1142	2873			A2		2001	1010	EP	2001-	11123	13		19	9811	24
E	P 1142	2873			A3		2003	0910								
E	P 1142	2873			В1		2004	0421								
	R:	BE,	DE,	ES,	FR,	GB,	IT,	SI,	LT, L	V, RO						
E	P 1142	2874			A2		2001	1010	EP	2001-	1112	14		19	9811	24
E	P 1142	2874			A3		2003	1022								
	R:	BE,	DE,	ES,	FR,	GB,	IT,	SI,	LT, L	V, RO						
									ES							
E	S 2221	1875			Т3		2005	0116	ES							
PRIORI	TY APE	PLN.	INFO	. :						1997-						
										1998-					9810	
										1998-						
									EP	1998-	1221:	14	A3	19	9811	24
AR T	he tit	le n	roce	88 0	omor:	ises	. e.	τ	conden	sation	of 4	4-0x	iranvl	met	hoxv	-9H-

- NB The title process comprises, e.g., condensation of 4-oxiranylmethoxy-9Hcarbazole with 2-(MeO)C6H4OCH2CH2NHCH2Ph in a protic organic solvent followed by deprotection.
- IT 3246-03-5P
- RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation of carvedilo1)
- RN 3246-03-5 HCAPLUS
- CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

- IT 51997-51-4, 4-Oxiranylmethoxy-9H-carbazole 95093-95-1,
 - (S)-4-Oxiranylmethoxy-9H-carbazole 95093-96-2,
 - (R)-4-Oxiranylmethoxy-9H-carbazole
 - RL: RCT (Reactant); RACT (Reactant or reagent)
- (preparation of carvedilol)
- RN 51997-51-4 HCAPLUS
- CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

RN 95093-95-1 HCAPLUS

CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.

RN 95093-96-2 HCAPLUS

CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

REFERENCE COUNT:

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1994:270010 HCAPLUS

DOCUMENT NUMBER: 120:270010

TITLE: Synthesis of the enantiomers and three racemic metabolites of Carvedilol labeled to high specific

activity with tritium

AUTHOR(S): Senderoff, S. G.; Villani, A. J.; Landvatter, S. W.;

Garnes, K. T.; Heys, J. R.

CORPORATE SOURCE: Dep. Synth. Chem., SmithKline Beecham Pharm., King of Prussia, PA. 19406, USA

SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals

(1993), 33(12), 1091-105

Τ

CODEN: JLCRD4; ISSN: 0362-4803

DOCUMENT TYPE: Journal LANGUAGE: English

LANGUAGE:

OCH2CH(OH)CH2NHCH2CH2C

Carvedilol (SK&F 105517) (I) possesses unique cardiovascular activity, and is under development for indications such as angina and hypertension. Tritium labeled enantiomers of Carvedilol and racemates of three metabolites were needed for pharmacol. and drug metabolic studies. These compds. were synthesized by catalytic tritium-halogen exchange using tritium gas and 10% palladium-on-carbon catalyst. The precursors were polyhalogenated in the carbazole ring. Direct electrophilic bromination of the enantiomers of Carvedilol gave precursors that were converted to the corresponding tritiated final products by catalytic tritium halogen exchange. Bromination of 4-(2,3-epoxypropyloxy)-9H-carbazole gave an intermediate that was converted to the halogenated precursors of the racemic metabolites. Elaboration of this intermediate, 1,3,6-tribromo-4-(2,3-epoxypropyloxy)-9H-carbazole, to the desired metabolite precursors was achieved by nucleophilic epoxide opening with suitably functionalized N-benzyl aryloxyethylamines. Catalytic tritium-halogen exchange upon the brominated metabolite precursors was accompanied by cleavage of N- and O-benzyl protecting groups. Radiochem. purities of all tritiated final products were greater than 98% after preparative HPLC. Specific activities of the final products, determined by mass spectrometry, ranged from 35 to 76 Ci/mmol. Optical purity of the Carvedilol enantiomers, determined by chiral HPLC, was greater than 99%.

IT 154582-49-7P 154582-52-2P 154582-53-3P 154582-56-6P 154582-57-7P

RL: SPN (Synthetic preparation); PREP (Preparation)

(intermediate in preparation of tritium labeled Carvedilol)

RN 154582-49-7 HCAPLUS

CN 9H-Carbazole, 1.3.6-tribromo-4-(oxiranvlmethoxy)- (9CI) (CA INDEX NAME)

RN 154582-52-2 HCAPLUS CN Phenol, 4-methoxy-3-[2-[(phenylmethyl)amino]ethoxy]-, 4-methylbenzenesulfonate (ester) (9CI) (CA INDEX NAME)

- RN 154582-53-3 HCAPLUS
- CN Phenol, 4-methoxy-3-[2-[(phenylmethyl)amino]ethoxy]- (CA INDEX NAME)

- RN 154582-56-6 HCAPLUS
- CN Phenol, 3-methoxy-4-[2-[(phenylmethyl)amino]ethoxy]-, 4-methylbenzenesulfonate (ester) (9CI) (CA INDEX NAME)

154582-57-7 HCAPLUS RN

CN Phenol, 3-methoxy-4-[2-[(phenylmethyl)amino]ethoxy]- (CA INDEX NAME)

тт 51997-51-4

RL: RCT (Reactant); RACT (Reactant or reagent)

(reactant, in preparation of tritium labeled Carvedilol)

RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

L13 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1980:128716 HCAPLUS

DOCUMENT NUMBER: 92:128716

ORIGINAL REFERENCE NO.: 92:20983a,20986a

TITLE: Carbazolyl-4-oxypropanolamine derivatives INVENTOR(S):

Wiedemann, Fritz; Kampe, Wolfgang; Thiel, Max; Sponer,

Gisbert; Roesch, Egon; Dietmann, Karl

PATENT ASSIGNEE(S): Boehringer Mannheim G.m.b.H., Fed. Rep. Ger.

Ger. Offen., 27 pp. SOURCE:

CODEN: GWXXBX DOCUMENT TYPE:

Patent LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2815926	A1	19791018	DE 1978-2815926	19780413
CA 1129416	A1	19820810	CA 1979-324667	19790402
DK 7901419	A	19791014	DK 1979-1419	19790406
DK 154555	В	19881128		
DK 154555	C	19890619		

FI	790114	12			A		19791014	F	Ι	1979-1142		19790406
FI	70406				В		19860327					
FI	70406				C		19860912					
AU	794582	20			A		19791018	Αl	J	1979-45820		19790406
AU	522975	5			B2		19820708					
ES	479396	ó			A1		19800416	E	3	1979-479396		19790406
SU	810079	9			A3		19810228	St	J	1979-2745301		19790406
EP	4920				A1		19791031	E	2	1979-101063		19790407
EP	4920				B1		19810805					
	R: E	ΒE,	CH,	DE,	FR,	GB,	IT, LU,	NL, S	SΕ			
IL	57020				A		19820730			1979-57020		19790408
DD	143607	7			A5		19800903	DI)	1979-212096		19790409
	227007				B2		19840416			1979-2434		19790410
	541575				A.		19791212	JI	?	1979-43119		19790411
JP	010234	162			В		19890502					
	790173	32			A		19800528			1979-1732		19790411
	21840				A2		19820227	H	J	1979-B01774		19790412
	179433				В		19821028					
	790276				A		19840115	A.	Γ	1979-2762		19790412
	375639				В		19840827					
	227047				B2		19840416			1982-6106		19820820
	450306				A		19850305			1983-479921		19830404
	632584				A		19881025			1987-76548		19870331
PRIORIT:	Y APPLN	1. I	NFO	. :						1978-2815926	A	19780413
										1979-21394		19790316
										1979-2434		19790410
									3	1980-198975	A1	19801021
OTHER S	OURCE (S	3):			MARE	AT	92:12871	6				

- * STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY AVAILABLE VIA OFFLINE PRINT *
- AB A wide range of I (R = H, lower alkyl, or aroyl; Rl = H, lower alkyl, or aralkyl, R2 and R3 independently were H or lower alkyl, X = CH2, O, S, or valence bond; Ar = mono- or bicyclic aryl or pyridyl) (.apprx.50 compds.) were prepared as B-sympatholytics and vasodilators (no data), in most cases by reaction of 4-(oxiranylmethoxy)carbazole (II) with an amine. Thus, 6.0 g II and 7.6 g 2-MeOC6H4CH2CH2NH2 were stirred 20 h at 70° to give 618 III. Also prepared were, e.g., IV and V.
- IT 3246-03-5

GI

- RL: RCT (Reactant); RACT (Reactant or reagent)
 (reaction of, with (oxiranylmethoxy)carbazole)
- RN 3246-03-5 HCAPLUS
- CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

IT 51997-51-4

RL: RCT (Reactant); RACT (Reactant or reagent)

(reaction of, with amines)

RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

=> d 114 ibib abs hitstr tot

L14 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:1154673 HCAPLUS

DOCUMENT NUMBER: 142:93675

TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-

[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-o1
INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev;

Thennati, Rajamannar

PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India

SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

P	ΑΊ	ENT I	.00			KIN	D	DATE		i	APPL	ICAT	ION I	NO.		D	ATE	
W	0	2004	1132	96		A1	_	2004	1229	1	WO 2	004-	IN52			2	0040	304
		W:										BG,						
			CN,	co,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FΙ,	GB,	GD,
			GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	ΚZ,	LC,
			LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NA,	NI,
	NO, NZ,					PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,
	TJ, TM, T					TR.	TT.	TZ.	UA.	UG.	US.	UZ.	VC.	VN.	YU.	ZA.	ZM.	ZW
	RW: BW, GH, G																	
			W: BW, GH, (BY, KG, I															
												MC,						
			SK,	TR,	BF,	BJ,	CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,	NE,	SN,
			TD.	TG														
I	IN 2003MU00647					A		2005	0211		IN 2	003-1	4U64	7		2	0030	620
U	US 2006270858					A1		2006	1130	- 1	US 2	005-	5539	57		2	0051	019
PRIORI	RIORITY APPLN. INFO.:										IN 2	003-1	4U64	7		A 2	0030	620
											IN 2	003-1	4U72	1		A 2	0030	717
										1	NO 2	004-	IN52		1	W 2	0040	304

- * STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY AVAILABLE VIA OFFLINE PRINT *
- The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrousZnCl2, and 50 q (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and
- the product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).
- 3246-03-5, N-[2-[2-(Methoxy)phenoxy]ethyl]benzylamine 51997-51-4, 4-(Oxiranylmethoxy)-9H-carbazole 95093-95-1, (S)-4-(Oxiranvlmethoxv)-9H-carbazole 95093-96-2,
 - (R)-4-(Oxiranvlmethoxy)-9H-carbazole
 - RL: RCT (Reactant); RACT (Reactant or reagent)
 - (reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and
 - hydrogenolysis of N-benzylcarvedilol)
- RN 3246-03-5 HCAPLUS
- CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

- RN 51997-51-4 HCAPLUS
- 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

RN 95093-95-1 HCAPLUS

CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.

RN 95093-96-2 HCAPLUS

CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

REFERENCE COUNT:

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:556143 HCAPLUS

DOCUMENT NUMBER: 137:125080

TITLE: Process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temperatures and

catalyst loading

INVENTOR(S): Scalone, Michelangelo; Zeibig, Thomas Albert

PATENT ASSIGNEE(S): Hoffmann-LaRoche Inc., Switz. SOURCE: U.S. Pat. Appl. Publ., 19 pp.

CODEN: USXXCO DOCUMENT TYPE: Patent.

LANGUAGE: English FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	TENT						DATE					TION				ATE	
	2002											-5446				0020	
116	6777	550	23		D2		2002	0017		05	2002	3440	2		-	0020	122
03	2434	100			3.1		2004	0017		0.3	2002	2121	100		-	0000	1 2 2
	2002																
	2002									WO	2002	-EP58	3		4	0020	122
WO																	
	w:											BR,					
												ES,					
												KP,					
												MX,					
		PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SI	, TJ	TM,	TR,	TT,	TZ,	UA,	UG,
		UZ,	VN,	YU,	ZA,	ZW											
	RW:	GH,	GM,	KE,	LS,	MW,	MZ,	SD,	SL,	SZ	, TZ	. UG,	ZM,	ZW,	ΑT,	BE,	CH,
		CY,	DE,	DK,	ES,	FI,	FR,	GB,	GR,	ΙE	, IT	LU,	MC,	NL,	PT,	SE,	TR,
		BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	GÇ	, GW	ML,	MR,	NE,	SN,	TD,	TG
	2002																
EP	1355	880			A2		2003	1029		EP	2002	-7166	73		2	0020	122
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GF	, IT	LI,	LU,	NL,	SE,	MC,	PT,
		IE.	SI.	LT.	LV.	FI.	RO.	MK.	CY.	AL	, TR						
JP	2004	5194	65		T		2004	0702		JΡ	2002	-5593	91		2	0020	122
IN	2003	CN01	126		A		2005	0422		IN	2003	-CN11	26		2	0030	722
MX	2003	PA06	606		A		2003	0922		MX	2003	-PA66	0.6		2	0030	723
	2004																
IIS	7169	935			B2		2007	0130									
PRIORIT	Y APP	T.N	TNFO					0100		EP	2001	-1015	84		A 2	0010	125
11.101.11	11.1		11.1	• •								-5446					
												-EP58					
OTHER S	OURCE	(S):			CASI	REAC	T 13	7:12								0020	122

AB A process for the preparation heterocyclic indene analogs, especially with the preparation

of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves

cyclocarbonylation followed by saponification This process avoids high temps. and

high catalyst loadings.

51997-51-4P, 4-Oxiranylmethoxy-9H-carbazole

RL: IMF (Industrial manufacture); PREP (Preparation)

(process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)

51997-51-4 HCAPLUS RN

9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

тт 3246-03-5

REFERENCE COUNT:

RL: RCT (Reactant); RACT (Reactant or reagent) (process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps, and catalyst loading)

3246-03-5 HCAPLUS RN

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

4 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2008 ACS on STN ACCESSION NUMBER: 1994:270010 HCAPLUS

DOCUMENT NUMBER: 120:270010

TITLE: Synthesis of the enantiomers and three racemic

metabolites of Carvedilol labeled to high specific activity with tritium

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS

AUTHOR(S): Senderoff, S. G.; Villani, A. J.; Landvatter, S. W.;

Garnes, K. T.; Heys, J. R.

CORPORATE SOURCE: Dep. Synth. Chem., SmithKline Beecham Pharm., King of Prussia, PA, 19406, USA

SOURCE: Journal of Labelled Compounds and Radiopharmaceuticals

(1993), 33(12), 1091-105

CODEN: JLCRD4; ISSN: 0362-4803

DOCUMENT TYPE: Journal

LANGUAGE: English GI

- AB Carvedilol (SK&F 105517) (I) possesses unique cardiovascular activity, and is under development for indications such as angina and hypertension. Tritium labeled enantiomers of Carvedilol and racemates of three metabolites were needed for pharmacol. and drug metabolic studies. These compds. were synthesized by catalytic tritium-halogen exchange using tritium gas and 10% palladium-on-carbon catalyst. The precursors were polyhalogenated in the carbazole ring. Direct electrophilic bromination of the enantiomers of Carvedilol gave precursors that were converted to the corresponding tritiated final products by catalytic tritium halogen exchange. Bromination of 4-(2,3-epoxypropyloxy)-9H-carbazole gave an intermediate that was converted to the halogenated precursors of the racemic metabolites. Elaboration of this intermediate. 1,3,6-tribromo-4-(2,3-epoxypropyloxy)-9H-carbazole, to the desired metabolite precursors was achieved by nucleophilic epoxide opening with suitably functionalized N-benzyl aryloxyethylamines. Catalytic tritium-halogen exchange upon the brominated metabolite precursors was accompanied by cleavage of N- and O-benzyl protecting groups. Radiochem. purities of all tritiated final products were greater than 98% after preparative HPLC. Specific activities of the final products, determined by mass spectrometry, ranged from 35 to 76 Ci/mmol. Optical purity of the Carvedilol enantiomers, determined by chiral HPLC, was greater than 99%.
- IT 154582-49-7P 154582-52-2P 154582-53-3P 154582-56-6P 154582-57-7P
 - RL: SPN (Synthetic preparation); PREP (Preparation)
 (intermediate in preparation of tritium labeled Carvedilol)
- RN 154582-49-7 HCAPLUS
- CN 9H-Carbazole, 1,3,6-tribromo-4-(oxiranylmethoxy)- (9CI) (CA INDEX NAME)

- RN 154582-52-2 HCAPLUS
- CN Phenol, 4-methoxy-3-[2-[(phenylmethyl)amino]ethoxy]-, 4-methylbenzenesulfonate (ester) (9CI) (CA INDEX NAME)

- RN 154582-53-3 HCAPLUS
- CN Phenol, 4-methoxy-3-[2-[(phenylmethyl)amino]ethoxy]- (CA INDEX NAME)

- RN 154582-56-6 HCAPLUS
- CN Phenol, 3-methoxy-4-[2-[(phenylmethyl)amino]ethoxy]-, 4-methylbenzenesulfonate (ester) (9CI) (CA INDEX NAME)

- RN 154582-57-7 HCAPLUS
- CN Phenol, 3-methoxy-4-[2-[(phenylmethyl)amino]ethoxy]- (CA INDEX NAME)

- IT 51997-51-4
 - RL: RCT (Reactant); RACT (Reactant or reagent)
- (reactant, in preparation of tritium labeled Carvedilol)
- RN 51997-51-4 HCAPLUS
- CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

=> d 115 ibib abs hitstr tot

L15 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:1154673 HCAPLUS

DOCUMENT NUMBER: 142:93675

TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol

Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar INVENTOR(S):

PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India PCT Int. Appl., 27 pp.

SOURCE:

CODEN: PIXXD2 DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION:

PATEN				KIN										DATE			
					_									-			
WO 20	041132	296		A1		2004	1229		WO 2	004-	IN52			2	0040	304	
W	: AE	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,	
	CN.	co,	CR.	CU.	CZ.	DE.	DK.	DM.	DZ.	EC.	EE.	EG.	ES.	FI.	GB.	GD.	
		GH,															
		LR,															
		NZ,															
	TJ, TM, TI					TZ,	UA,	UG,	US,	UΖ,	VC,	VN,	YU,	ZA,	ZM,	ZW	
R	RW: BW, GH, GM					MW,	MZ,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	AZ,	
	BY.	KG,	KZ.	MD.	RU.	TJ.	TM.	AT.	BE.	BG.	CH.	CY.	CZ.	DE.	DK.	EE.	
		FI.															
		TR,															
			DF,	ъ,	CF,	cu,	C1,	CP1,	GA,	GIV,	σQ,	GW,	PIL,	PIP.,	INE.	ON,	
		TG		_								_		_			
IN 20															0030		
US 20	062701	358		A1		2006	1130		US 2	005-	5539	57		2	0051	019	
PRIORITY A	PRIORITY APPLN. INFO.:								IN 2	003-	MU64	7		A 2	0030	620	
							IN 2	003-	MU72	1		A 2	0030	717			
		WO 2004-INS															
OTHER COME		CASREACT 142:93675; MARPAT 142:93675								0010	001						
CINER SOUR	(0)			CASREACI 142:936/3; MARPAI 142:936/3													

GI

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *
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The present invention provides a process for preparation of 1-[9H-carbazol-4-vloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnC12, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous laver was separated.

and the product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtoAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at

temperature

RN

 $60\text{--}70^\circ$ for a period of about 10 h and filtered. The filtrate was concentrated to remove EtoAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 3246-03-5, N-[2-[2-(Methoxy)phenoxy]ethyl]benzylamine

- 51997-51-4, 4-(Oxiranylmethoxy)-9H-carbazole 95093-95-1,
- (S)-4-(Oxiranylmethoxy)-9H-carbazole 95093-96-2,
- (R)-4-(Oxiranylmethoxy)-9H-carbazole
- RL: RCT (Reactant); RACT (Reactant or reagent)

(reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

- 3246-03-5 HCAPLUS
- CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

- RN 51997-51-4 HCAPLUS
- CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

RN 95093-95-1 HCAPLUS

CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.

RN 95093-96-2 HCAPLUS

CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

REFERENCE COUNT:

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L17 ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2007:38855 HCAPLUS

DOCUMENT NUMBER: 146:142505

TITLE: Process for preparation of carvedilol

INVENTOR(S): Kumar, Ashok; Saxena, Ashvini; Bhattacharvva, Anindva; Singh Sengar, Amit Vikram; Pathak, Gunjan Pramod; Soudagar, Satish Rajanikant; Mathur, Pramil Kumar; Nijasure, Avinash Manohar; Salunke, Sanjukumar

Motiram; Gautam, Prashant; Ramsingh, Thakur Gajendrasingh; Jadhav, Dilip Uttam

PATENT ASSIGNEE(S): IPCA Laboratories Ltd., India

SOURCE:

Eur. Pat. Appl., 11pp. CODEN: EPXXDW

DOCUMENT TYPE: Patent. LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION:

	PATENT NO.						D	DATE			APE	LI	CAT:	I NOI	NO.		DATE			
							-										-			
	EP	1741	700			A1		2007	0110		EP	20	06-3	1167.	52		2	20060706		
		R:	AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE	Ξ, Ι	ES,	FI,	FR,	GB,	GR,	HU,	IE,	
			IS,	IT,	LI,	LT,	LU,	LV,	MC,	NL,	PΙ	, 1	PΤ,	RO,	SE,	SI,	SK,	TR,	AL,	
			BA,	HR,	MK,	YU														
	IN	2005	MU00	807		A		2007	0629					08UM			2	0050	706	
	US	2007	0272	02		A1		2007	0201		US	20	06-4	4805	26		2	0060	705	
PRIC	TIRC	Y APP	LN.	INFO	. :						IN	20	05-1	MU80	7	- 2	A 2	0050	706	
OTH	ER S	DURCE	(S):			CASI	REAC	T 14	6:14	2505										
3.5		1_																		

AB Disclosed herein is a process for preparation of carvedilol free from impurity, which comprises reaction of 4-(2,3-epoxypropoxy)carbazole with 2-(2-methoxyphenoxy)ethylamine in a polar aprotic solvent, followed by isolation of carvedilol as an acid addition salt and subsequent conversion into pure carvedilol.

918903-19-2P 918903-21-6P 918903-23-8P

918903-28-3P RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediate; preparation of carvedilol)

918903-19-2 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, 4-methylbenzenesulfonate (1:?) (CA INDEX NAME)

CM 1

CRN 72956-09-3 CMF C24 H26 N2 O4

PAGE 1-A

PAGE 2-A

CM 2

CRN 104-15-4 CMF C7 H8 O3 S

RN 918903-21-6 HCAPLUS CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, sulfate (1:?) (CA INDEX NAME)

CM 1

CRN 72956-09-3 CMF C24 H26 N2 O4

PAGE 1-A

PAGE 2-A

CM 2

CRN 7664-93-9 CMF H2 O4 S

но- s- он

RN 918903-23-8 HCAPLUS

CN 2-Propanol, 1-(9H-carbazo1-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, acetate (1:?) (CA INDEX NAME)

CM 1

CRN 72956-09-3

CMF C24 H26 N2 O4

PAGE 1-A

PAGE 2-A

CM 2

CRN 64-19-7 CMF C2 H4 O2

HO- C- CH-

RN 918903-28-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, phosphate (1:?) (CA INDEX NAME)

CM 1

CRN 72956-09-3 CMF C24 H26 N2 O4

PAGE 1-A

PAGE 2-A

MeO

CM 2

CRN 7664-38-2 CMF H3 **04 P**

T 72956-09-3P, Carvedilol RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation) (preparation of carvedilol)

RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 1-A

PAGE 2-A

RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2006:558278 HCAPLUS

DOCUMENT NUMBER: 145:62782

TITLE: Process for the preparation of carvedilol or its enantiomers from the ring-opening reaction of

4-(2,3-epoxypropoxy) carbazole or its enantiomers with an excess of 2-(2-methoxyphenoxy) ethylamine in ethyl

acetate as the reaction solvent

INVENTOR(S): Trepat Guixer, Elisenda; Munoz Alvarez, Anna; Pomares
Marco, Marta; Marquillas Olondriz, Francisco

PATENT ASSIGNEE(S): Zambon Group S.p.A., Italy

SOURCE: PCT Int. Appl., 11 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent

DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	PATENT NO.					KIND DATE			APPLICATION NO.						DATE			
	2006				A1	_	2006	0615		WO 2	005-1	EP56	469		2	0051	205	
	W:	ΑE,	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,	
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,	
		GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KM,	KN,	KP,	KR,	
		KZ,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	LY,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	
		MZ,	NA,	NG,	NI,	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	
		SG,	SK,	SL,	SM,	SY,	TJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	
		VN,	YU,	ZA,	ZM,	ZW												
	RW:	AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	IE,	
		IS,	IT,	LT,	LU,	LV,	MC,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR,	BF,	BJ,	
		CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,	NE,	SN,	TD,	TG,	BW,	GH,	
		GM,	KE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	AZ,	BY,	
		KG,	KZ,	MD,	RU,	TJ,	TM											
CA	2589	699			A1		2006	0615		CA 2	005-	2589	699		2	0051	205	
EP	1838	670			A1	A1 20071003			B EP 2005-815876					20051205				
	R:	ΑT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	IE,	

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IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU

WO 2005-EP56469

W 20051205

CN 101072753 A 20071114 CN 2005-80042214 20051205 IN 2007C002478 A 20070907 IN 2007-CN2478 20070611 PRIORITY APPLN. INFO: EP 2004-106438 A 20041209

OTHER SOURCE(S): CASREACT 145:62782

B A process for the preparation of carvedilol, as well as its optically active R and S enantiomers, comprises the ring-opening reaction of 4-(2,3-epoxypropoxy) carbazole, or its enantiomers, with an excess of 2-(2-methoxyphenoxy)ethylamine using Et acetate as the reaction solvent.

T 5190/2-51-04 1-4(2,3-Epoxypropoxylarabasole 95093-951)

IT 51997-51-4, 4-(2,3-Epoxypropoxy)carbazole 95093-95-1 95093-96-2

RL: RCT (Reactant); RACT (Reactant or reagent)

(process for the preparation of carvedilol or its enantiomers from the ring-opening reaction of 4-(2,3-epoxypropoxy)carbazole or its enantiomers with an excess of 2-(2-methoxyphenoxy)ethylamine in Et acetate as the reaction solvent)

RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranvlmethoxv)- (CA INDEX NAME)

RN 95093-95-1 HCAPLUS

CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.

RN 95093-96-2 HCAPLUS

CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

IT 72956-09-3P, Carvedilol 95093-99-5P, (R)-Carvedilol
95094-00-1P, (S)-Carvedilol

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(process for the preparation of carvedilol or its enantiomers from the ring-opening reaction of $4-(2,3-\mathrm{epo},\mathrm{ypropoxy})$ carbacole or its enantiomers with an excess of $2-(2-\mathrm{methoxyphenoxy})$ ethylamine in Et acetate as the reaction solvent

RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 1-A

PAGE 2-A

RN 95093-99-5 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RN 95094-00-1 HCAPLUS

Absolute stereochemistry. Rotation (-).

REFERENCE COUNT:

2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:1335682 HCAPLUS

DOCUMENT NUMBER: 146:274158

TITLE: A modified process to obtain Carvedilol

AUTHOR(S): Anon.

CORPORATE SOURCE: Spain

SOURCE: IP.com Journal (2005), 5(11A), 34 (No. IPCOM000130550D), 26 Oct 2005

CODEN: IJPOBX; ISSN: 1533-0001

PUBLISHER: IP.com, Inc. DOCUMENT TYPE: Journal; Patent

LANGUAGE: English

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IP 130550D		20051026		
PRIORITY APPLN. INFO.:			IP 2005-130550D	2005102

CASREACT 146:274158

OTHER SOURCE(S):

Carvedilol [i.e., 1-(9H-carbazol-4-vloxv)-3-[[2-(2-AB

methoxyphenoxy)ethyl]amino]-2-propanol], a β-adrenergic blocker, is obtained by the reaction of 4-[(2-oxiranvl)methoxvl-9H-carbazole with 2-(2-methoxyphenoxy)ethylamine hydrochloride in the presence of potassium carbonate in toluene solvent. In this process the byproduct [i.e., a dimer, 1,1'-[[2-(2-methoxyphenoxy)ethyl]imino]bis[3-(9H-carbazol-4-yloxy)-2-propanol]] is reduced to less than one percent. Carvedilol

thus prepared meets EP specifications with only one crystallization 72956-09-3P, Carvedilol

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(process for preparation of carvedilol (minimizing byproduct formation) using [(oxiranyl)methoxy]carbazole with (methoxyphenoxy)ethylamine hydrochloride as starting materials, potassium carbonate as reagent and toluene as solvent)

RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 1-A

PAGE 2-A

IT 51997-51-4, 4-Oxiranylmethoxy-9H-carbazole RL: RCT (Reactant); RACT (Reactant or reagent) (process for preparation of carvedilol (minimizing byproduct formation) using [(oxiranyl)methoxylcarbazole with (methoxyphenoxylethylamine hydrochloride as starting materials, potassium carbonate as reagent and toluene as solvent)
RN 51997-51-4 HOAPLIS

RN 51997-51-4 HCAPLUS CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

L17 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:1288806 HCAPLUS

DOCUMENT NUMBER: 144:22811

TITLE: A novel process for the preparation of

1-(9H-carbazol-4-yloxy)-3-[[2-(-methoxyphenoxy)-ethyl] amino]-propan-2-ol (carvedilol)

INVENTOR(S): Tarur, Venkatasubramanian Radhakrishnan; Sathe,

Dhananjay Govind; Kulkarni, Swapnil Jayant
PATENT ASSIGNEE(S): USV Limited, India
SOURCE: PCT Int. Appl., 14 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION:

PATENT	NO.	KIND DATE			LICATI	ON NO.		DATE			
	115981 115981		20051208	WO	2005-1	IN139		20050503			
	AE, AG, AL, CN, CO, CR, GE, GH, GM, LC, LK, LR, NI, NO, NZ, SM, SY, TJ,	AM, AT CU, CZ HR, HU LS, LT OM, PG	, AU, AZ, , DE, DK, , ID, IL, , LU, LV, , PH, PL,	BA, BE DM, DZ IN, IS MA, ME PT, RC	, EC, , JP, , MG,	EE, EG, KE, KG, MK, MN, SC, SD,	ES, FI KM, KF MW, MX SE, SG	, GB, GD, , KR, KZ, , MZ, NA, , SK, SL,			
RW:	ZM, ZW BW, GH, GM, AZ, BY, KG, EE, ES, FI, RO, SE, SI,	KE, LS KZ, MD FR, GB SK, TR	, MW, MZ, , RU, TJ, , GR, HU, , BF, BJ,	NA, SE TM, AT IE, IS), SL, , BE,	SZ, TZ, BG, CH, LT, LU,	UG, ZM CY, CZ MC, NL	I, ZW, AM, , DE, DK, , PL, PT,			
		A A1	20060616	US IN WO	2006-5 2004-N	MU479 568732 MU479 IN139	A	20040422 20061227 20040422 20050503			

04/18/2008

GI

- AB This invention disclosed a novel process for preparation of carvedilol (I) in high purity by using eco friendly solvents. The process comprised reacting 4-hydroxycarbazole with epichlorhydrin in presence of an organic solvent and a base at temps. between 10° and 30°, and then reacting the resultant 4-(2,3-epoxypropoxy)carbazole with a salt of 2-(2-methoxyphenoxy)ethylamine, preferably the hydrochloride salt, in presence of a base and a hydroxylic solvent at temps. between 30° and 90°.
- temps: Detween 30° and 30°.

 72956-09-3P, 1-(9H-Carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]propan-2-ol
 RL: RMF (Industrial manufacture); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)
 (eco friendly process for the preparation of carvedilol, a pharmaceutically useful adrenergic B-receptor antagonist)
- RN 72956-09-3 HCAPLUS CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 1-A

PAGE 2-A

MeO.

51997-51-4P, 4-(2,3-Epoxypropoxy)carbazole

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(eco friendly process for the preparation of carvedilol, a pharmaceutically useful adrenergic β -receptor antagonist)

RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

L17 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2005:1260624 HCAPLUS

DOCUMENT NUMBER: 144:22806

TITLE: Process for the preparation of carvedilol

INVENTOR(S): Kankan, Rajendra Narayanrao; Rao, Dharmaraj Ramachandra

PATENT ASSIGNEE(S):

Cipla Limited, India; Wain, Christopher Paul SOURCE: PCT Int. Appl., 29 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA:	TENT	NO.			KIND DATE				APPLICATION NO.						DATE			
						_												
WO	WO 2005113502				A1 20051201				WO 2	005-	GB19	78		20050519				
	W:	ΑE,	AG,	AL,	AM,	AT,	AU,	ΑZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,	
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,	
		GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KM,	KP,	KR,	KZ,	
		LC,	LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NA,	
		NG,	NI,	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	

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SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU,
             ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
             EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT,
             RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
                                20051201
                                            AU 2005-245182
     AU 2005245182
                          A1
                                                                    20050519
     CA 2566197
                          A1
                                20051201
                                            CA 2005-2566197
                                                                    20050519
     EP 1756057
                          A1
                                20070228
                                            EP 2005-744187
                                                                    20050519
           AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
             IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR
     JP 2007538061
                          Т
                                20071227
                                            JP 2007-517424
                                                                    20050519
     IN 2006MN01302
                                20070608
                                            IN 2006-MN1302
                                                                    20061107
                          Α
PRIORITY APPLN. INFO.:
                                            GB 2004-11273
                                                                 A 20040520
                                            WO 2005-GB1978
                                                                 W 20050519
OTHER SOURCE(S):
                        CASREACT 144:22806
```

ОН OMe

A process for the preparation of carvedilol I (R = H) was disclosed AR and comprised aromatization/reduction of 1,2,3,9-tetrahydro-4H-carbazol-4-one by refluxing with Raney Ni and NaOH in water for 20 h to form 4-hydroxy-9H-carbazole, reaction of resulting alc. with epichlorohydrin using tetrabutylammonium bromide and NaOH in water to give 4-oxiranylmethoxy-9H-carbazole, reaction of the intermediate epoxide with MeO-2-C6H4O(CH2)2NHCH2Ph using K2CO3 in water to give carvedilol N-benzvl derivative I (R = CH2Ph), and finally, debenzylation of I (R = CH2Ph) using Pd/C in EtOAc and water to give the desired carvedilol. This invention further provided carvedilol prepared by the disclosed process, and pharmaceutical compns. containing the same, for therapeutic uses, such as adrenergic β-receptor antagonists, vasodilators and treatment of angina pectoris.

72956-09-3P, Carvedilol TТ

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(preparation of carvedilol for use in pharmaceutical compns. as adrenergic β-receptor antagonists and vasodilators useful for the treatment of hypertension and angina pectoris)

RN

72956-09-3 HCAPLUS
2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-CN (CA INDEX NAME)

PAGE 2-A

MeO.

51997-51-4P, 4-Oxiranylmethoxy-9H-carbazole

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of carvedilol for use in pharmaceutical compns. as adrenergic β -receptor antagonists and vasodilators useful for the treatment of hypertension and angina pectoris)

- 51997-51-4 HCAPLUS
- CN
- 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

RN

REFERENCE COUNT:

THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN

1

ACCESSION NUMBER: 2005:1128799 HCAPLUS

DOCUMENT NUMBER: 143:386916

TITLE: An improved process for the manufacture of

carvedilol
INVENTOR(S): Kankan, Rajendra Narayan Rao; Rao, Dharamraj

Ramchandra
PATENT ASSIGNEE(S): Cipla Ltd., India

SOURCE: Indian, 11 pp.
CODEN: INXXAP

DOCUMENT TYPE: Patent LANGUAGE: English

LANGUAGE: Englis FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 186587	A1	20011006	IN 1999-B0583	19990817
PRIORITY APPLN. INFO.:			IN 1999-B0583	19990817
OTHER SOURCE(S):	CASREA	CT 143:38691	6; MARPAT 143:386916	

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB An improved process for the manufacture of Carvedilol I, a potent antinypertensive (no biol. data given) by catalytic hydrogenation of N-substituted Carvedilol II [RI = (un)substituted CH2Ph; formed by reacting carbacole III with a substituted amine IVI. Thus, N-alkylating benzylamine with 2-(2-methoxyphenoxy)ethyl bromide followed by reaction of the resulting N-[2-(2-methoxyphenoxy)ethyl]benzenemethanamine hydrochloride with 4-(2,3-epoxypropoxy)carbazole, and subsequent hydrogenation of the II [RI = Ch2Ph] afforded carvedilol I.

IT 72956-09-3P, Carvedilol

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(improved process for the manufacture of carvedilol)

- RN 72956-09-3 HCAPLUS
- CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 1-A

PAGE 2-A

- RN 51997-51-4 HCAPLUS
- CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

L17 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN ACCESSION NUMBER: 2005:962205 HCAPLUS

DOCUMENT NUMBER: 143:266815

TITLE:

Process for the manufacture of racemic

carvedilol from 4-(oxiran-2-ylmethoxy)-9H-carbazole
and 2-(2-methoxyphenoxy)ethylamine

INVENTOR(S): Shah, Dhiraj R.; Naik, Ashish P.; Purohit, Parva Y.; Sharma, Rajivkumar; Agarwal, Virendra Kumar

PATENT ASSIGNEE(S): Cadila Healthcare Limited, India

SOURCE:

PCT Int. Appl., 14 pp. CODEN: PIXXD2 Patent

DOCUMENT TYPE: Patent LANGUAGE: English FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA:	PATENT NO.				KIND DATE		APPLICATION NO.							ATE				
	2005						2005 2006									0050	222	
		CN, GE, LK, NO, TJ, BW, AZ, EE, RO,	CO, GH, LR, NZ, TM, GH, BY, ES, SE,	CR, GM, LS, OM, TN, GM, KG, FI, SI,	CU, HR, LT, PG, TR, KE, KZ, FR, SK,	CZ, HU, LU, PH, TT, LS, MD, GB, TR,	AU, DE, ID, LV, PL, TZ, MW, RU, GR, BF,	DK, IL, MA, PT, UA, MZ, TJ, HU,	DM, IN, MD, RO, UG, NA, TM, IE,	DZ, IS, MG, RU, US, SD, AT, IS,	EC, JP, MK, SC, UZ, SL, BE, IT,	EE, KE, MN, SD, VC, SZ, BG, LT,	EG, KG, MW, SE, VN, TZ, CH, LU,	ES, KP, MX, SG, YU, UG, CY, MC,	FI, KR, MZ, SK, ZA, ZM, CZ, NL,	GB, KZ, NA, SL, ZM, ZW, DE, PL,	GD, LC, NI, SY, ZW, AM, DK, PT,	SM
CA EP	MR, NE, SN, IN 2004MU00219 CA 2560353 EP 1723107 R: AT, BE, BG, IS, IT, LI, HR, LV, MK, PRIORITY APPLN. INFO::				A A1 A2 CH, LT, YU	CY,	MC,	0901 1122 DE, NL,	DK, PL,	CA 2 EP 2 EE, PT, IN 2 WO 2	005- 005- ES, RO, 004-	2560 7473 FI, SE, MU21 IN56	353 43 FR, SI,	GB, SK,	GR, TR,	0050 0050 HU, AL,	222 222 IE, BA,	
	UED GOUDGE (G)																	

OTHER SOURCE(S): CASREACT 143:266815; MARPAT 143:266815

AB Carvedilol of high HPLC purity (>99.5 %) is prepared by the ring-opening

addition reaction of 4-(oxiran-2-ylmethoxy)-9H-carbazole with 2-(2-methoxyphenoxy)ethylamine followed by salification of the impure carvedilol with an organic acid (e.g., salicylic acid) and neutralization of the carvedilol salt (e.g., carvedilol salicylate) with a base to give pure carvedilol.

IT 787598-89-4P, Carvedilol oxalate 787598-91-8P,

Carvedilol salicylate 863664-91-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(in a process for the manufacture of racemic carvedilol from 4-(oxiran-2-ylmethoxy)-9H-carbazole and 2-(2-methoxyphenoxy)ethylamine)

RN '87598-89-4 HCAPLUS
CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-,
ethanedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 72956-09-3 CMF C24 H26 N2 O4

PAGE 1-A

PAGE 2-A

MeO

CM 2

CRN 144-62-7 CMF C2 H2 O4

0 0 || || HO-C-C-OH

RN 787598-91-8 HCAPLUS

CN Benzoic acid, 2-hydroxy-, compd. with 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol (1:1) (CA INDEX NAME)

CM 1

CRN 72956-09-3 CMF C24 H26 N2 O4

PAGE 1-A

PAGE 2-A

CM 2

CRN 69-72-7 CMF C7 H6 O3

RN CN

863664-91-9 HCAPLUS 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2R, 3R)-2,3-dihydroxybutanedioate (1:1) (salt) (9C1) (CA INDEX NAME)

CM

CRN 72956-09-3

CMF C24 H26 N2 O4

PAGE 1-A

PAGE 2-A

CM 2

CRN 87-69-4 CMF C4 H6 O6

Absolute stereochemistry.

OH

IT 72956-09-3P, Carvedilol

RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (process for the manufacture of racemic carvedilol from 4-(oxiran-2-ylmethoxy)-9H-carbazole and 2-(2-methoxyphenoxy)ethylamine)

RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 2-A

IT 51997-51-4

RN

RL: RCT (Reactant); RACT (Reactant or reagent)
(process for the manufacture of racemic carvedilol from
4-(oxiran-2-ylmethoxy)-9H-carbazole and 2-(2-methoxyphenoxy)ethylamine)
51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

L17 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:1154673 HCAPLUS

DOCUMENT NUMBER: 142:93675

A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-TITLE:

methoxyphenoxy)ethyl]amino]propan-2-o1

INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar

PATENT ASSIGNEE(S):

Sun Pharmaceutical Industries Limited, India PCT Int. Appl., 27 pp.

SOURCE: CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

	NO.	KIND	DATE		ION NO.	DATE			
		A1	20041229			20040304			
W:	CN, CO, CR GE, GH, GM LK, LR, LS	CU, CZ, HR, HU, LT, LU,	DE, DK, ID, IL, LV, MA,	DM, DZ, EC, IN, IS, JP, MD, MG, MK,	EE, EG, ES KE, KG, KE MN, MW, MX	(, BZ, CA, CH, S, FI, GB, GD, P, KR, KZ, LC, K, MZ, NA, NI, G, SK, SL, SY,			
RW:	TJ, TM, TN BW, GH, GM BY, KG, KZ ES, FI, FR	TR, TT, KE, LS, MD, RU, GB, GR,	TZ, UA, MW, MZ, TJ, TM, HU, IE,	UG, US, UZ, SD, SL, SZ, AT, BE, BG, IT, LU, MC,	VC, VN, YU TZ, UG, ZN CH, CY, CZ NL, PL, PT	J, ZA, ZM, ZW 4, ZW, AM, AZ, Z, DE, DK, EE, I, RO, SE, SI, L, MR, NE, SN,			
	MU00647 270858								
OTHER SOURCE	(S):	CASREAC	T 142:93	-WO 2004 575; MARPAT		W 20040304			

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the

- * STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY AVAILABLE VIA OFFLINE PRINT *
- AR The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]aminol-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranvlmethoxv)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous laver was separated, and

product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

- IT 72956-09-3P, Carvedilol 95093-99-5P,
 - $\label{eq:capacity} $$(R)=-(3H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-ol 95094-00-1P, (S)-1-(9H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-ol $$$(methoxy)phenoxylethyl]amino]propan-2-ol $$$$$
 - RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
 - (preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)
- RN 72956-09-3 HCAPLUS
- CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino](CA INDEX NAME)

PAGE 1-A

PAGE 2-A

RN 95093-99-5 HCAPLUS

Absolute stereochemistry. Rotation (+).

RN 95094-00-1 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

- T 51997-51-4, 4-(Oxiranylmethoxy)-9H-carbazole 95093-95-1,
 - (S)-4-(Oxiranylmethoxy)-9H-carbazole 95093-96-2,
 - (R)-4-(Oxiranylmethoxy)-9H-carbazole
 - RL: RCT (Reactant); RACT (Reactant or reagent)

(reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N- (methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

- RN 51997-51-4 HCAPLUS
- CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

RN 95093-95-1 HCAPLUS

CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.

RN 95093-96-2 HCAPLUS

CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

REFERENCE COUNT:

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:927171 HCAPLUS

DOCUMENT NUMBER: 141:395415

TITLE: Process for the preparation of crystalline

carvedilol form-II

INVENTOR(S): Ramanjaneyulu, Gorantla Seeta; Kumar, Indukuri Venkata Sunil; Rao, Ketavarapu Narasimha; Kishore, Jammula

Vera Venkata Krishna

PATENT ASSIGNEE(S): Matrix Laboratories Ltd., India

SOURCE: PCT Int. Appl., 18 pp.

SOURCE: PCT Int. Appl., IN CODEN: PIXXD2

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	PATENT NO.						KIND DATE		APPLICATION NO.						DATE 20040416				
	WO					A1		2004	1104							2	0040	416	
		W:	ΑE,	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,	
			CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,	
			GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KZ,	LC,	
			LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NA,	NI,	
			NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,	
	TJ, TM, T				TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW	
		RW:	BW,	GH,	GM,	KE,	LS,	MW,	MZ,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	AZ,	
			BY,	KG.	KZ,	MD,	RU,	TJ,	TM.	AT,	BE.	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	
			TD,	TG															
	IN	2003	MAO 0	328		A		2007	0518	IN 2003-MA328						20030421			
	EP	1615	888			A1		2006	0118		EP 2	004-	7279	71		2	0040	416	
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	US 2007055069									US 2	005-	5528	43		2	0051	012		
PRIO	PRIORITY APPLN. INFO.:							IN 2003-MA328					A 2	0030	421				
										WO 2004-IN104				1	W 2	0040	NA, NI, SL, SY, ZM, ZW AM, AZ, DK, EE, SI, NE, SN, 030421 040416 MC, PT, PL, SK, HI 051012 030421		

OTHER SOURCE(S): CASREACT 141:395415

B The present invention provides a cost-effective, industrially feasible process for the manufacture of crystalline carvedilol form-II using novel carvedilol salts comprising a step of reacting 4-(2,3-epoxypropoxy)carbazole with 2-(2-methoxyphenoxy)ethylamine followed by acidification with mineral acid in presence of an organic solvent to yield acid addition salts, (e.g. carvedilol oxalate), treatment of the said salts with base(s) in presence of organic solvent(s), water, and isolation from the organic solvent(s) followed by crystallization from Et acetate.

IT 72956-09-3P, Carvedilol

RL: IMF (Industrial manufacture); PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)

(preparation of crystalline carvedilol form-II by reaction of 4-(2,3-epoxypropoxy)carbazole with 2-(2-methoxyphenoxy)ethylamine)

RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 1-A

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IT 51997-51-4P, 4-(2,3-Epoxypropoxy)carbazole 787598-89-4P,
Carvedilol oxalate 787598-91-8P, Carvedilol salicylate
R1: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic
preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of crystalline carvedilol form-III by reaction of
4-(2,3-epoxypropoxy)carbazole with 2-(2-methoxyphenoxy)ethylamine)

4-(2,3-epoxypropoxy)Carbazole with 2-(2-methoxypnehoxy)ethylamine RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

RN CN

787598-89-4 HCAPLUS 2-Fropanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, ethanedioate (1:1) (salt) (9C1) (CA INDEX NAME)

CM 1

CRN 72956-09-3 CMF C24 H26 N2 O4

PAGE 1-A

PAGE 2-A

CM 2

CRN 144-62-7 CMF C2 H2 O4

RN 787598-91-8 HCAPLUS

CN Benzoic acid, 2-hydroxy-, compd. with 1-(9H-carbazo1-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2-propanol (1:1) (CA INDEX NAME)

CM

CRN 72956-09-3 CMF C24 H26 N2 O4

PAGE 1-A

PAGE 2-A

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS

MeO

CM 2

CRN 69-72-7 CMF C7 H6 03

CO₂H

REFERENCE COUNT:

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:412919 HCAPLUS

DOCUMENT NUMBER: 140:406735

TITLE: Process for the preparation of carvedilol from 4-(oxirane-2-ylmethoxy)-9H-carbazole and

INVENTOR(S):

(Comments of the control of the con

PATENT ASSIGNEE(S): Zentiva, A.S., Slovakia

SOURCE: PCT Int. Appl., 13 pp. CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PA:	TENT	NO.			KIN	D :	DATE			APPL	ICAT	ION	NO.		D	ATE		
WO	2004				A1		2004	0521		WO 2	003-	SK20			2	0031	104	
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		LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NI,	NO,	NZ,	OM,	
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		ES,	FI,	FR,	GB,	GR,	HU,	IE,	IT,	LU,	MC,	NL,	PT,	RO,	SE,	SI,	SK,	
		TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,	NE,	SN,	TD,	Τ
SΚ	2855	47			В6		2007	0301		SK 2	002-	1595			2	0021	108	
ΑU	2003	3018	61		A1		2004	0607		AU 2	003-	3018	61		2	0031	104	

04/18/2008 Page 74

EP 1558575 20050803 EP 2003-810732 20031104 A1 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK US 2006167077 A1 20060727 US 2005-533809 20050505 PRIORITY APPLN. INFO .: SK 2002-1595 A 20021108 WO 2003-SK20 W 20031104

OTHER SOURCE(S): CASREACT 140:406735

Carvedilol is prepared in high yield and selectivity by the reaction of 4-(oxirane-2-ylmethoxy)-9H-carbazole with acid-addition salts of 2-(2-methoxyphenoxy) ethylamine [e.g., 2-(2-methoxyphenoxy) ethylamine hydrochloride] in the presence of a base (e.g., potassium carbonate) in an C2-5 alc. solvent (e.g., isopropanol) at an elevated temperature (e.g., 33°).

IT 72956-09-3P, Carvedilol

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(process for the preparation of carvedilol from
4-(oxirane-2-ylmethoxy)-9H-carbazole and 2-(2-methoxyphenoxy)ethylamine

salts) RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 1-A

PAGE 2-A

ΙT 51997-51-4

> RL: RCT (Reactant); RACT (Reactant or reagent) (process for the preparation of carvedilol from 4-(oxirane-2-ylmethoxy)-9H-carbazole and 2-(2-methoxyphenoxy)ethylamine

salts)

RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

L17 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:556143 HCAPLUS

DOCUMENT NUMBER: 137:125080

TITLE: Process for preparing heterocyclic indene

analogs by cyclocarbonylation at moderate temperatures

and catalyst loading

INVENTOR(S): Scalone, Michelangelo; Zeibig, Thomas Albert

PATENT ASSIGNEE(S): Hoffmann-LaRoche Inc., Switz. SOURCE: U.S. Pat. Appl. Publ., 19 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT	NO.			KIN	D	DATE		APPL	ICAT	ION I	NO.	 D.	ATE	
US 2002 US 6777		23		A1 B2		2002 2004		US 2	002-	5446	2	2	0020	122
CA 2434 WO 2002	408	20		A1 A2		2002 2002	0801		002-				0020	
	05908	39		A3		2002	1031							
W:	0 2002059089 W: AE, AG, A CO, CR, C													

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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
            LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
            PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
            UZ, VN, YU, ZA, ZW
        RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
            CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
            BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG
    AU 2002247645
                              20020806 AU 2002-247645
                         A1
                               20031029 EP 2002-716673
    EP 1355880
                         A2
                                                                20020122
        R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
    JP 2004519465
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                                         JP 2002-559391
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    IN 2003CN01126
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                                          IN 2003-CN1126
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    MX 2003PA06606
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                                        MX 2003-PA6606
                                                                 20030723
    US 2004127723
                        A1
                              20040701
                                         US 2004-763296
                                                                 20040122
    US 7169935
                        B2 20070130
                                          EP 2001-101584
                                                              A 20010125
PRIORITY APPLN. INFO.:
                                          US 2002-54462
                                                              A3 20020122
                                           WO 2002-EP583
                                                              W 20020122
                       CASREACT 137:125080; MARPAT 137:125080
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OTHER SOURCE(S):

A process for the preparation heterocyclic indene analogs, especially with the preparation of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves cyclocarbonylation followed by saponification This process avoids high temps, and high catalyst loadings,

51997-51-4P, 4-Oxiranylmethoxy-9H-carbazole 72956-09-3P,

Carvedilol

RN

RL: IMF (Industrial manufacture); PREP (Preparation) (process for preparing heterocyclic indene analogs by

cyclocarbonylation at moderate temps. and catalyst loading) 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

72956-09-3 HCAPLUS RN

2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 1-A

PAGE 2-A

MeO

REFERENCE COUNT: THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD, ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: DOCUMENT NUMBER:

2002:10275 HCAPLUS

TITLE: INVENTOR(S): 136:90914

Preparation of carvedilol and its crystalline hydrate and solvate

Hildesheim, Jean; Finogueev, Sergey; Aronhime, Judith;

Dolitzky, Ben-Zion; Ben-Valid, Shoshana; Kor, Ilan

Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.

SOURCE: PCT Int. Appl., 42 pp.

CODEN: PIXXD2 Patent

DOCUMENT TYPE: LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION:

PATENT ASSIGNEE(S):

PA	TENT :	NO.			KIN		DATE				LICAT					DATE	
	2002	0000									2001-					20010	
WO											2001-						
	w:										, EE,						
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							51,	SK,	SL,	10	, TM,	IK,	11,	12,	UA	, UG,	US,
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um	2003										2003-	1802				20010	628
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CN	1733	727	21		7		2004	0215		CN	2005-	1008	50 6095			20010	628
FD	1655	285			7.1		2006	0510		FD	2005- 2005-	2110	5			20010	628
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											, TR	D1,	шо,	1127	01	, 110,	/
7.A	2002				A						2002-	1028	2			20021	219
											2002-						
IIS	2004	1527	57		A1		2004	0805		IIS	2004-	7580	25			20040	116
US	7056	942			B2		2006	0606		0.0	2004-					20010	110
US	2004	2251	32		A1		2004	1111		US	2004-	7580	26			20040	116
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US	2006	0306	14		A1		2006	0209		US	2005-	2176	43			20050	831
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PRIORIT											2000-						
										US	2000-	2463	58P		P	20001	107
										AU	2000-	2716	39		A3	20010	628
										CN	2001-	8146	16		A3	20010	628
										EP	2001-	9506	71		A3	20010	628
										US	2001-	8947	98		A3	20010	628
										WO	2001-	JS20	760		W	20010	628
										US	2004-	7580	25		A3	20040	116
AD Th	ia in	ront.	ion .			٠	n im		- 4 -			e nn		ina			

This invention relates to an improved process of preparing carvedilol, as well as a new crystalline hydrate and solvate and forms of carvedilol, processes for the manufacture thereof, and pharmaceutical compns. thereof. Carvedilol was prepared by the reaction of 2-(2-methoxyphenoxy)ethylamine and 4-(oxiran-2-ylmethoxy)-9H-carbazole.

Crystalline carvedilol form II was prepared by crystallizing carvedilol from isoamvl

- alc. 72956-09-3P, Carvedilol 385765-36-6P IT
 - RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of carvedilol and its crystalline hydrate and solvate)
- 72956-09-3 HCAPLUS
 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-CN (CA INDEX NAME)

PAGE 1-A

PAGE 2-A

RN 385765-36-6 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, hydrochloride, hydrate (9CI) (CA INDEX NAME)

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PAGE 2-A

x HCl

●x H₂O

IT 51997-51-4 RE: RCT (Reactant); RACT (Reactant or reagent) (preparation of carvedilol and its crystalline hydrate and solvate) 51997-51-4 HCAPLUS RN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME) CN

REFERENCE COUNT:

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN ACCESSION NUMBER: 2001:747161 HCAPLUS

3

DOCUMENT NUMBER: 135:288689

DOCUMENT NUMBER: 135:288689

TITLE: Process for preparing 1-[9'H-carbazol-4'yloxy]-3-[2"-(2"'- methoxyphenoxy)ethylamino]-propan-2-

yloxy|5-|2-(2-- methoxyphenoxy)ethylamino|-propan-2ol [carvedilol]
INVENTOR(S): Ratkai. Zoltan: Barkoczy. Jozsef: Simig. Gyula:

NVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyoergyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy,

Peter Kotay; Seres, Peter

PATENT ASSIGNEE(S): Egis Gyogyszergyar Rt., Hung. SOURCE: Eur. Pat. Appl., 11 pp.

CODEN: EPXXDW DOCUMENT TYPE: Patent

LANGUAGE: English FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND DATE	APPLICATION NO.	DATE
EP 1142873	A2 20011010	EP 2001-111213	19981124
EP 1142873	A3 20030910		
EP 1142873	B1 20040421		
R: BE, DE, ES,	FR, GB, IT, SI,	LT, LV, RO	
HU 9802180	A1 20001228	HU 1998-2180	19981001
RU 2216539	C2 20031120	RU 1998-120700	19981118
RU 2245875	C2 20050210	RU 2003-107772	19981118
EP 918055	A1 19990526	EP 1998-122114	19981124
EP 918055	B1 20030423		
EP 918055	B2 20060426		
R: AT, BE, CH,	DE, DK, ES, FR,	GB, GR, IT, LI, LU, NL,	SE, MC, PT,
IE, SI, LT,	LV, FI, RO		
PRIORITY APPLN. INFO.:		HU 1997-2209	A 19971124
		HU 1998-2180	A 19981001
		EP 1998-122114	A3 19981124
		RII 1998-120700	A 19981118

OTHER SOURCE(S): CASREACT 135:288689

AB A process for preparing 1-[9'H-carbazo1-4'-yloxy]-3-[{2'-(2'-

methoxyphenoxy)ethyl}amino|propan-2-ol as well as acid addition salts of this compound, was developed in which the N-[2-(2'-methoxy-phenoxy)ethyl]benzylamine is reacted with epichlorohydrin, and the formed 1-N-benzy1-2'-[{(2'-methoxy-phenoxy)ethy1}amino]-3-propan-2-ol is reacted with 4-hydroxy-9H-carbazole and the resulting 1-N-benzy1-2'-(methoxyphenoxyethylamino) -3-[9'H-carbazol-4'-yloxy]propan-2-ol is debenzylated by catalytic hydrogenation and, if desired, the 1-[9'H-carbazol-4'-vloxv]-3-[{2'-(2'-methoxyphenoxy)ethyl}amino]propan-2ol thus obtained is reacted with acids to vield acid addition their salts, or if desired, liberating the free 1-[9'H-carbazol-4'-yloxy]-3-[{2}-(2'methoxyphenoxy)ethyl]aminopropan-2-ol base from acid addition salts thereof and, if desired, converting the free 1-[9'H-carbazol-4'-yloxy]-3-{2}-(2'methoxyphenoxy)ethylamino-propan-2-ol base into other acid addition salts and/or, if desired, separating the enantiomers.

72956-09-3P, Carvedilol

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(process for preparing 1-[9'H-carbazol-4'-vloxy]-3-[2-(2'methoxyphenoxy)ethylamino[propan-2-ol [carvedilol])

RN

72956-09-3 HCAPLUS 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-CN (CA INDEX NAME)

PAGE 1-A

PAGE 2-A

MeO

IT 51997-51-4

RL: RCT (Reactant); RACT (Reactant or reagent) (process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[2-(2'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])

RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

L17 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1999:344783 HCAPLUS

DOCUMENT NUMBER: 130:352184

TITLE: Preparation of carvedilol

INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyorgyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor;

Balazzio; Doman, Imre; Greff, Zoltan; Nagy,

Peter Kotay; Seres, Peter PATENT ASSIGNEE(S): Eqis Gyoqyszergyar Rt., Hung.

Eur. Pat. Appl., 17 pp.

Page 84

CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

SOURCE:

PA'	TENT	NO.			KIN	D	DATE			APF	LICA	ΙTΑ	ON I	NO.		D	ATE	
						-												
EP	9180	55			A1		1999	0526		EΡ	1998	3-1	221:	14		13	9981	124
EP	9180	55			B1		2003	0423										
EP	9180	55			B2		2006	0426										
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GF	, 11	,	LI,	LU,	NL,	SE,	MC,	PT,
			SI,	LT,	LV,													
HU	9802	180			A1		2000	1228		HU	1998	3-2	180			1:	9981	001

CZ	296521			В6	20060	3412	CZ	1998-3561		19981104
CZ	297445			В6	2006:	1213	CZ	2004-1111		19981104
HR	980590			B1	2003	1231	HR	1998-590		19981112
SK	284109			В6	20040	3908	SK	1998-1560		19981112
RU	2216539	9		C2	2003:	1120	RU	1998-120700		19981118
RU	2245875	5		C2	20050	0210	RU	2003-107772		19981118
EP	1142873	3		A2	2001	1010	EP	2001-111213		19981124
EP	1142873	3		A3	20030	0190				
EP	1142873	3		В1	20040	3421				
	R: BI	E, DE,	ES,	FR,	GB, IT,	SI,	LT, L	/, RO		
	114287			A2	2001	1010	EP	2001-111214		19981124
EP	114287	4		A3	2003	1022				
	R: BI	E, DE,	ES,	FR,	GB, IT,	SI,	LT, LV	/, RO		
ES	2196459	9		Т3	2003:	1216	ES	1998-122114		19981124
ES	2221875	ō		Т3	20050)116	ES	2001-111213		19981124
PRIORIT	Y APPLN	. INFO	. :				HU	1997-2209	A	19971124
							HU	1998-2180	A	19981001
							RU	1998-120700	A	19981118
							EP	1998-122114	A3	19981124
AD The	a + i + l a	nroco		omer	icoc o	~ /	andone	ation of		

- AB The title process comprises, e.g., condensation of 4-oxiranylmethoxy-9H-carbazole with 2-(MeO)CGH4OCH2CH2NHCH2Ph in a protic organic solvent followed by deprotection.
- TT 72956-09-3P, Carvedilol 95093-99-5P, (+)-Carvedilol 95094-00-1P, (-)-Carvedilol
 - RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
 - (preparation of carvedilol)
- RN 72956-09-3 HCAPLUS
- CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino](CA INDEX NAME)

PAGE 1-A

PAGE 2-A

RN 95093-99-5 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RN 95094-00-1 HCAPLUS

Absolute stereochemistry. Rotation (-).

IT 51997-51-4, 4-Oxiranylmethoxy-9H-carbazole 95093-95-1,

- (S)-4-0xiranylmethoxy-9H-carbazole 95093-96-2,
 - (R)-4-0xiranylmethoxy-9H-carbazole
- RL: RCT (Reactant); RACT (Reactant or reagent) (preparation of carvedilol)
- RN 51997-51-4 HCAPLUS
- CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

- RN 95093-95-1 HCAPLUS
- CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.

- RN 95093-96-2 HCAPLUS
- CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

REFERENCE COUNT:

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L18 ANSWER 1 OF 6 HCAPLUS COPYRIGHT 2008 ACS on STN

2

ACCESSION NUMBER: 2005:1260624 HCAPLUS

DOCUMENT NUMBER: 144:22806

TITLE: Process for the preparation of carvedilol INVENTOR(S): Kankan, Rajendra Narayanrao; Rao, Dharmaraj

Ramachandra

PATENT ASSIGNEE(S): Cipla Limited, India; Wain, Christopher Paul

SOURCE: PCT Int. Appl., 29 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

	ENT				KIN	D	DATE					ION I			D	ATE	
	2005				A1	-	2005	1201							2	0050	519
	W:	ΑE,	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,
							DE,										
							ID,										
		LC,	LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	ΜZ,	NΑ,
		NG,	NI,	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,
		SL,	SM,	SY,	ΤJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,
		ZA,	ZM,	zw													
	RW:	BW,	GH,	GM,	KE,	LS,	MW,	MZ,	NA,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,
		AZ,	BY,	KG,	KZ,	MD,	RU,	TJ,	TM,	AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,
		EE,	ES,	FI,	FR,	GB,	GR,	HU,	IE,	IS,	IT,	LT,	LU,	MC,	NL,	PL,	PT,
		RO,	SE,	SI,	SK,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,
		MR,	NE,	SN,	TD,	TG											
ΑU	2005	2451	82		A1		2005	1201		AU 2	005-	2451	82		2	0050	519
CA	2566	197			A1		2005	1201		CA 2	005-	2566	197		2	0050	519
EP	1756	057			A1		2007	0228	1	EP 2	005-	7441	87		2	0050	519
	R:	AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,	ES,	FI,	FR,	GB,	GR,	HU,	IE,
		IS,	IT,	LI,	LT,	LU,	MC,	NL,	PL,	PT,	RO,	SE,	SI,	SK,	TR		
JΡ	2007	5380	61		T		2007	1227		JP 2	007-	5174:	24		2	0050	519
IN	2006	MN01	302		A		2007	0608		IN 2	006-	MN13	02		2	0061	107

04/18/2008 Page 88

PRIORITY APPLN. INFO.:

GB 2004-11273 WO 2005-GB1978 A 20040520

OTHER SOURCE(S):

CASREACT 144:22806

Ι

WO 2003 GD1370

W 20050519

O OH NR OME

- AB A process for the preparation of carvedilol I (R = H) was disclosed and comprised aromatization/reduction of 1,2,3,9-tetrahydro-4H-carbazol-4-one by refluxing with Raney Ni and NaOH in water for 20 h to form 4-hydroxy-9H-carbazole, reaction of resulting alc. with epichlorohydrin using tetrabutylammonium bromide and NaOH in water to give 4-oxiranylmethoxy-9H-carbazole, reaction of the intermediate epoxide with MeO-2-C6H40(CH2/2NhCH2/Ph using KZCO3 in water to give carvedilol N-benzyl derivative I (R = CH2/Ph), and finally, debenzylation of I (R = CH2/Ph) using Pd/C in EtoRa and water to give the desired carvedilol. This invention further provided carvedilol prepared by the disclosed process, and pharmaceutical compns. containing the same, for therapeutic uses, such as adrenergic B-receptor antagonists, vasodilators and treatment of anging pectoris.
 - IT 72956-09-3P, Carvedilol RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
 - (preparation of carvedilol for use in pharmaceutical compns. as adrenergic β -receptor antagonists and vasodilators useful for the treatment of hypertension and angina pectoris)
- RN 72956-09-3 HCAPLUS
- CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 1-A

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MeO

3246-03-5

RL: RCT (Reactant); RACT (Reactant or reagent) (preparation of carvedilol for use in pharmaceutical compns. as adrenergic β -receptor antagonists and vasodilators useful for the treatment

of hypertension and angina pectoris) RN

3246-03-5 HCAPLUS CN

Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

REFERENCE COUNT:

THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

1 L18 ANSWER 2 OF 6 HCAPLUS COPYRIGHT 2008 ACS on STN

04/18/2008

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ACCESSION NUMBER: 2005:1128799 HCAPLUS

DOCUMENT NUMBER: 143:386916

TITLE: An improved process for the manufacture of

carvedilol

INVENTOR(S): Kankan, Rajendra Narayan Rao; Rao, Dharamraj

Ramchandra

PATENT ASSIGNEE(S): Cipla Ltd., India SOURCE: Indian, 11 pp.

CODEN: INXXAP
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
IN 186587	A1	20011006	IN 1999-B0583	19990817
PRIORITY APPLN. INFO.:			IN 1999-B0583	19990817
OTHER SOURCE(S):	CASRE	ACT 143:38691	6: MARPAT 143:386916	

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- * STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY AVAILABLE VIA OFFLINE PRINT *
- AB An improved process for the manufacture of Carvedilol I, a potent antihypertensive (no biol. data given) by catalytic hydrogenation of N-substituted Carvedilol II [Rl = (un)substituted CH2Ph; formed by reacting carbazole III with a substituted amine IV]. Thus, N-alkylating benzylamine with 2-(2-methoxyphenoxy)ethyl bromide followed by reaction of the resulting N-[2-(2-methoxyphenoxy)ethyl]benzenemethanamine hydrochloride with 4-(2,3-epoxypropoxy)carbazole, and subsequent hydrogenation of the II [Rl = Ch2Ph] afforded carvedilol I.
- II 120606-08-8P RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
- (improved process for the manufacture of carvedilo1)
 RN 120606-08-8 HCAPLUS
- CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]-, hydrochloride (9CI) (CA INDEX NAME)

HC1

IT 72956-09-3P, Carvedilol

 ${\tt RL:}\ {\tt IMF}\ ({\tt Industrial\ manufacture})\ ;\ {\tt SPN}\ ({\tt Synthetic\ preparation})\ ;\ {\tt PREP}\ ({\tt Preparation})$

(improved process for the manufacture of carvedilol)

- RN 72956-09-3 HCAPLUS
- CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

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- IT 3246-03-5
 - RL: RCT (Reactant); RACT (Reactant or reagent)
 (improved process for the manufacture of carvedilol)
- RN 3246-03-5 HCAPLUS
- CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

L18 ANSWER 3 OF 6 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:1154673 HCAPLUS

DOCUMENT NUMBER: 142:93675

TITLE: A process for preparation of 1-[9H-carbazo1-4-yloxy]-3-[[2-(2-

methoxyphenoxy)ethyl]amino]propan-2-ol

INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev;

Thennati, Rajamannar

PATENT ASSIGNEE(S): Sun Pharmaceutical Industries Limited, India

SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

	ENT				KIN	D	DATE			APPL	ICAT	ION I	NO.		D	ATE	
	2004				A1		2004	1229		WO 2	004-	IN52			2	0040	304
	W:	AE,	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,
		CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,
		GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KZ,	LC,
		LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NA,	NI,
		NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,
		TJ,	TM,	TN,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VC,	VN,	YU,	ZA,	ZM,	ZW
	RW:	BW,	GH,	GM,	KE,	LS,	MW,	MZ,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AM,	AZ,
		BY,	KG,	KZ,	MD,	RU,	TJ,	TM,	AT,	BE,	BG,	CH,	CY,	CZ,	DE,	DK,	EE,
		ES,	FI,	FR,	GB,	GR,	HU,	IE,	IT,	LU,	MC,	NL,	PL,	PT,	RO,	SE,	SI,
		SK,	TR,	BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,	NE,	SN,
		TD,	TG														
IN	2003	0 0 UM	647		A		2005	0211		IN 2	003-	MU64	7		2	0030	620
US	2006	2708	58		A1		2006	1130		US 2	005-	5539.	57		2	0051	019
PRIORITY	APP	LN.	INFO	. :						IN 2	003-	MU64	7		A 2	0030	620
										IN 2	003-	MU72	1		A 2	0030	717
										WO 2	004-	IN52			W 2	0040	304
OTHER SC	URCE	(S):			CAS	REAC	T 14	2:93	675;	MAR	PAT	142:	9367	5			

AB The present invention provides a process for preparation of 1-[9H-carbaxol-4-yloxy]-3-[2-(2-methoxyphenoxy) ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein RI = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein RI is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy|pthyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for

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^{*} STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

checking conversion to N-benzylcarvedilo1), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and

the

CN

product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in ELOAC, 7 g wet 5% Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature $60-70^\circ$ for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 72956-09-3P, Carvedilol 95093-99-5P,

 $\label{eq:continuous} $$(R)-1-(9H-Carbazo1-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-ol $$9094-00-1P, ($)-1-(9H-Carbazo1-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-ol $$$(methoxy)-phenoxylethyl]amino]propan-2-ol $$$$$

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

RN 72956-09-3 HCAPLUS

2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

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PAGE 2-A

RN 95093-99-5 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

RN 95094-00-1 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

IT 3246-03-5, N-[2-[2-(Methoxy)phenoxy]ethyl]benzylamine

RL: RCT (Reactant); RACT (Reactant or reagent) (reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

3246-03-5 HCAPLUS RN

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

REFERENCE COUNT: 2

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 4 OF 6 HCAPLUS COPYRIGHT 2008 ACS on SIN ACCESSION NUMBER: 2002:556143 HCAPLUS

DOCUMENT NUMBER: 137:125080

TITLE:

Process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temperatures

and catalyst loading

Scalone, Michelangelo; Zeibig, Thomas Albert INVENTOR(S): PATENT ASSIGNEE(S):

Hoffmann-LaRoche Inc., Switz. SOURCE: U.S. Pat. Appl. Publ., 19 pp.

CODEN: USXXCO Patent

DOCUMENT TYPE: LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

US	2002	0992	23		A1		2002	0725	1								
										CA 2	002-	2434	408		2	0020	122
										-							
										BB.	BG.	BR.	BY,	BZ.	CA.	CH,	CN.
												,			-	,	
	RW:	GH,	GM,	KE,	LS,	MW,	MZ,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AT,	BE,	CH,
		CY,	DE,	DK,	ES,	FI,	FR.	GB,	GR.	IE,	IT,	LU,	MC,	NL,	PT,	SE,	TR,
		BF,	ВJ,	CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,	NE,	SN,	TD,	TG
AU	2002	2476	45		A1		2002	0806		AU 2	002-	2476	45		2	0020	122
EP	1355	880			A2		2003	1029	1	EP 2	002-	7166	73		2	0020	122
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	IT,	LI,	LU,	NL,	SE,	MC,	PT,
		IE,	SI,	LT,	LV,	FI,	RO,	MK,	CY,	AL,	TR						
JP	2004	5194	65		T		2004	0702		JP 2	002-	5593	91		2	0020	122
IN	2003	CN01	126		A		2005	0422		IN 2	003-	CN11:	26		2	0030	722
MX	2003	PA06	606		A		2003	0922	1	MX 2	003-	PA66	06		2	0030	723
US	2004	1277	23		A1		2004	0701	1	US 2	004-	7632	96		2	0040	122
US	7169	935			B2		2007	0130									
RITY	(APP	LN.	INFO	. :					1	EP 2	001-	1015	84		A 2	0010	125
									1	WO 2	002-	EP58	3	1	N 2	0020	122
	US US CA WO WO AU EP IN MX US US	AU 2002 EP 1355 R: JP 2004 IN 2003 W:	US 20020992 US 6777559 CA 2434408 WO 20020590 WC 20020590 WE 20020590 WE AE, CO, GM, LS, PT, UZ, RW: GH, CY, BE 1355880 R: AT, IE, JP 20045194 IN 2003CN01 US 7169935	US 2002099223 US 6777559 CA 2434408 WO 2002059089 WO 2002059089 WI AE, AG, CO, CR, GM, HR, LS, LT, PT, RO, UZ, VN, RN: GH, GM, CY, DE, BF, BJ, AU 2002247645 EP 1335880 R: AT, BE, JP 2004519465 IN 2003CN01126 US 2004127723 US 7169935	US 2002099223 US 6777559 CA 2434408 M0 2002059089 W1 AE, AG, AL, CC, CT, GM, HR, HU, LS, LT, LU, PT, RO, RU, UZ, VN, YU, RW: GH, GM, KE, CY, DE, DK, BF, BJ, CF, AU 2002247645 EF 1355880 R: AT, BE, CH, IE, SI, LT, JP 2004519465 MX 2003PA06606 MX 2003PA06606 MX 2003PA06606	No. No.	No. No.	S 2002099223	No. No.	US 2002099223 A1 20020725 US 6777559 B2 20040817 CA 2434408 A1 20020801 W0 2002059089 A2 20020801 W1 2002059089 A3 20021031 W1 AE, AG, AL, AM, AT, AU, AZ, BA, CO, CR, CU, CZ, DE, DK, DM, DZ, GM, HR, HU, ID, II, IN, IS, JF, LS, LT, LU, LV, MA, MD, MG, MK, PT, RO, RU, SD, SE, SG, SI, SK, UZ, VN, YU, ZA, ZW RNI GH, GM, KE, LS, MM, MZ, SD, SL, CY, DE, DK, ES, FI, FR, GB, GR, BF, BJ, CF, CG, CI, CM, GA, GN, AU 2002247645 A1 20020806 P1 1355880 A2 20031029 R: AT, BE, CH, DE, DK, ES, FR, GB, LT, LV, FIR, OM, KC, Y, JP 2004519465 I 20040702 MX 2003PA06606 A 2003922 MX 2003PA06606 A 2003922 MX 2003PA06606 A 20039922 MX 2003PA06606 A 20039922 MX 2003PA06606 A 20039928 RITY APPLN. INFO::	US 2002099223 A1 20020725 US 2 US 6777559 B2 20040817 CA 2434408 A1 20020801 CA 2 W0 2002059089 A2 20020801 W0 2 W1 AE, AG, AL, AM, AT, AU, AZ, BA, BB, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, GM, HR, HU, ID, IL, IN, IS, JP, KE, LS, LT, LU, LV, MA, MD, MG, MK, MT, PT, RO, RU, SD, SE, SG, SI, SK, SL, CY, DE, DK, ES, FI, FR, GB, GR, IE, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, AU 2002247645 A1 20020806 AU 2 R1 AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, SF, BJ, CF, CG, CI, CM, GA, GN, GQ, AU 2002247645 A1 20020806 AU EP 1355880 A2 20031029 EP 2 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, JP 2004519465 T 20040702 JP 2 IN 2003CN01126 A 20050422 IN 2 US 2004127723 A1 20040701 US 2 US 7169935 B2 20070130	US 2002099223 A1 20020725 US 2002- US 6777559 B2 20040817 CA 2434408 A1 20020801 CA 2002- W0 2002059089 A2 20020801 W0 2002- W1 AE, AG, AL, AH, AT, AU, AZ, BA, BB, BG,	US 2002099223 A1 20020725 US 2002-5446 US 6777559 B2 20040817 CA 2434408 A1 20020801 CA 2002-2434 W0 2002059089 A2 20020801 W0 2002-EP58 W1 AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, GM, HR, HU, ID, III, IN, 1S, JF, KE, KG, KF, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, FT, RO, RU, SD, SE, SG, SI, SK, SL, IJ, TM, UZ, VN, YU, ZA, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, BF, BJ, CF, CG, CI, CM, GA, GN, GO, GW, ML, AU 2002247645 A1 20020806 A0 2002-2476 BF 1355880 A2 20031029 BF 2002-7166 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, JF 2004519465 T 20040702 JP 2002-5593 MX 2003CN01126 A 20030422 IN 2003-EN11 MX 2003FA06606 A 20030922 MX 2003-F865 US 716933 A1 EVERTIFY APPLN: INFO::	US 2002099223 A1 20020725 US 2002-54462 US 6777559 B2 20040817 CA 2434408 A1 20020801 CA 2002-2434408 W0 2002059089 A2 20020801 W0 2002-EP583 W1 AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GM, HR, HU, ID, III, IN, IS, JF, KE, KG, KF, KR, FT, RO, RU, SD, SE, SG, SI, SK, SI, SI, TJ, TM, TM, UZ, VN, YU, ZA, ZW RWI CH, GM, KE, LS, MM, MZ, SD, SL, SZ, TZ, UG, ZM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, BF, BJ, CF, GC, CI, CM, GA, GM, GO, GW, MI, MC, AD, AD, CY, DE, DK, ES, FI, FR, GB, GR, IT, IT, LU, MC, BF, BJ, CF, GC, CI, CM, GA, GM, GO, GW, MI, MC, AD, CY, DE, DK, ES, FI, FR, GB, GR, IT, LT, LU, LU, LY, FI, RO, MK, CY, AL, TR JP 2004519465 T 20040702 US 2001127023 MX 2005PA66066 A 20030922 MX 2003-P569391 RITY APPLN. INFO.: EF 20070100	US 2002099223 A1 20020725 US 2002-54462 US 6777559 B2 20040817 CA 2434408 A1 20020801 CA 2002-2434408 W0 2002059089 A2 20020801 W0 2002-EP583 W1 AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GM, HR, HU, ID, IL, IN, IS, JF, KE, KG, KF, KR, KZ, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, PT, RO, RU, SD, SE, SG, SI, SS, LT, JJ, MT, RT, TL, UZ, VN, YU, ZA, ZW RN: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, BF, BJ, CF, CG, CI, CM, GA, GM, GQ, GW, ML, MR, NE, AU 2002247645 A1 20020806 A0 2002-247645 EP 1355880 A2 20031029 EP 2002-716673 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, JP 2004519465 T 20040702 JP 2002-559391 IN 2003CN01126 A 20050422 IN 2003-CN1126 MS 2003Pa06606 A 20039922 MS 2003-PA66006 US 2004127723 A1 20040701 US 2004-763296 RIXT APPLN. INFO:: EP 2001-101584 US 2002-54462 JE 2002-24462	US 2002099223 A1 20020725 US 2002-54462 2 US 6777559 B2 20040817 CA 2434408 A1 20020801 CA 2002-2434408 2 W0 2002059089 A2 20020801 W0 2002-EP583 2 W1 AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KF, KR, KZ, LO, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PT, RO, RU, SS, SE, SS, SI, SK, ST, JJ, TM, TR, TT, TT, UU, VV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PT, RO, RU, SS, SE, SS, SI, SK, ST, JJ, TM, TR, TT, TT, BF, GB, GR, IE, IT, LU, MC, NL, PT, BF, BJ, CFG, CI, CM, GA, GN, GQ, GW, MI, MR, MR, SV, SU 2002-247645 A1 20020806 AU 2002-247645 2 EP 135580 A2 20031029 EP 2002-716673 2 ER, AT, BE, CH, DE, DK, ES, FT, GB, GR, IT, LI, LU, NL, SE, LT, SI, SI, LT, LV, FT, RO, MK, CY, AL, TR JP 2004519465 T 20040702 JP 2002-555391 2 IN 2003CN01126 A 20050422 IN 2003-CN1126 2 US 2004127723 A1 20040701 US 2004-763286 2 US 20014127723 A1 20040701 US 2004-763286 2 ERITY APPLN. INFO::	US 2002099223

04/18/2008 Page 96

OTHER SOURCE(S): CASREACT 137:125080; MARPAT 137:125080

B A process for the preparation heterocyclic indene analogs, especially with the preparation of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves cyclocarbonylation followed by saponification This process

avoids high temps. and high catalyst loadings.
IT 72956-09-3P, Carvedilol

RL: IMF (Industrial manufacture); PREP (Preparation)
(process for preparing heterocyclic indene analogs by
cyclocarbonylation at moderate temps. and catalyst loading)

RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 1-A

NH

PAGE 2-A

IT 3246-03-5

RL: RCT (Reactant); RACT (Reactant or reagent) (process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)

RN 3246-03-5 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 6 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:747161 HCAPLUS

DOCUMENT NUMBER: 135:288689

TITLE: Process for preparing 1-[9'H-carbazol-4'-

yloxy]-3-[2"-(2"'- methoxyphenoxy)ethylamino]-propan-2-

ol [carvedilol]

INVENTOR(S): Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula;

Gregor, Tamas; Vereczkey, Gyoergyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor;

Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy,

Peter Kotay; Seres, Peter
PATENT ASSIGNEE(S): Eqis Gyogyszergyar Rt., Hung.

SOURCE: Eur. Pat. Appl., 11 pp. CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PA:	TENT NO.		F	KIND	DATE	APPLICATION NO.	DATE
			-				
EP	1142873			A2	20011010	EP 2001-111213	19981124
EP	1142873			A3	20030910		
EP	1142873			B1	20040421		
	R: BE,	DE,	ES, F	FR, GB,	IT, SI,	LT, LV, RO	
HU	9802180			A1	20001228	HU 1998-2180	19981001
RU	2216539			C2	20031120	RU 1998-120700	19981118
RU	2245875			C2	20050210	RU 2003-107772	19981118
EP	918055			A1	19990526	EP 1998-122114	19981124
EP	918055			B1	20030423		
EP	918055			B2	20060426		
	R: AT,	BE,	CH, E	DE, DK,	ES, FR,	GB, GR, IT, LI, LU, NL, S	SE, MC, PT,

IE, SI, LT, LV, FI, RO
PRIORITY APPLN. INFO:: HU 1997-2209 A 19971124
HU 1998-2180 A 19981001

HO 1998-2280 A 19981124 EP 1998-122114 A3 19981124 RU 1998-120700 A 19981118

OTHER SOURCE(S): CASREACT 135:288689

AB A process for preparing 1-[9'H-carbazol-4'-yloxy]-3-[(2'-(2'methoxyphenoxy)ethyl)amino]propan-2-ol as well as acid addition salts of this compound, was developed in which the N-[2-(2'-methoxy-phenoxy)ethyl]benzylamine is reacted with epichlorohydrin, and the formed 1-N-benzyl-2'-[((2'-methoxy-phenoxy)ethyl)amino]-3-propan-2-ol is reacted

with 4-hydroxy-9H-carbazole and the resulting 1-N-benzy1-2'- (methoxyphenoxyethylamino)-3-[9'H-carbazol-4'-yloxy]propan-2-ol is

(methoxyphenoxyethylamino)-3-[9'H-carbazol-4'-yloxy]propan-2-ol is debenzylated by catalytic hydrogenation and, if desired, the

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1-[9'H-carbazol-4'-yloxy]-3-[{2'-(2'-methoxyphenoxy)ethyl}amino]propan-2-ol thus obtained is reacted with acids to yield acid addition their salts, or if desired, liberating the free 1-[9'H-carbazol-4'-yloxy]-3-[{2}-(2'-methoxyphenoxy)ethyl]aminopropan-2-ol base from acid addition salts theref and, if desired, converting the free 1-[9'H-carbazol-4'-yloxy]-3-[2]-(2'-methoxyphenoxy)ethylamino-propan-2-ol base into other acid addition salts and/or, if desired, separating the enantiomers.

3246-03-5P 120606-08-8P RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (process for preparing 1-19'H-carbazol-4'-yloxy]-3-|2-(2'-methoxyphenoxy)ethylamino|propan-2-01 [carvedilo1])

RN 3246-03-5 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

RN 120606-08-8 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]-, hydrochloride (9CI) (CA INDEX NAME)

HC1

IT 72956-09-3P, Carvedilol

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(process for preparing 1-[9'H-carbazo1-4'-yloxy]-3-[2-(2'-methoxyphenoxy)ethylamino]propan-2-ol [carvedilol])

RN 72956-09-3 HCAPLUS CN 2-Propagol, 1-(9H-c

2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 1-A

PAGE 2-A

Me0

L18 ANSWER 6 OF 6 HCAPLUS COPYRIGHT 2008 ACS on STN ACCESSION NUMBER: 1999:344783 HCAPLUS

DOCUMENT NUMBER: 130:352184

TITLE: Preparation of carvedilol INVENTOR(S):

Ratkai, Zoltan; Barkoczy, Jozsef; Simig, Gyula; Gregor, Tamas; Vereczkey, Gyorgyi Donath; Nemeth, Norbert; Nagy, Kalman; Cselenyak, Judit; Szabo, Tibor; Balazs, Laszlo; Doman, Imre; Greff, Zoltan; Nagy,

Peter Kotay; Seres, Peter Egis Gyogyszergyar Rt., Hung. PATENT ASSIGNEE(S): SOURCE: Eur. Pat. Appl., 17 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

04/18/2008 Page 100

						-												
EP	9180	55			A1		1999	0526	EP	1	998-	1221	14			199	81:	124
EP	9180	55			В1		2003	0423										
	9180																	
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB, G	R,	IT,	LI,	LU,	NL,	SE	E, 1	1C,	PT,
							RO											
HU	9802 2965	180			A1		2000	1228	HU	1	998-	2180				199	810	001
CZ	2965	21			В6		2006	0412	CZ	1	998-	3561				199	81	104
CZ	2974	45			B6		2006	1213	CZ	2	004-	1111				199	81:	104
							2003	1231	HR	. 1	998-	590				199	81:	112
SK	2841	.09			B6		2004	0908	SK	1	998-	1560				199	81:	112
RU	2216	539			C2		2003	1120	RU									
	2245										003-							
									EP	2	001-	1112	13			199	81:	124
EP	1142	873			A3		2003	0910										
EP	1142	873			В1		2004	0421										
	R:	BE,	DE,	ES,	FR,	GB,	IT,	SI,	LT, L	v,	RO							
EP	1142	874			A2		2001	1010	EP	2	001-	1112	14			199	81:	124
EP	1142																	
	R:	BE,	DE,	ES,	FR,	GB,	IT,	SI,	LT, L	v,	RO							
ES	2196	459			Т3		2003	1216	ES	1	998-	1221	14			199	81:	124
					Т3		2005	0116	ES									
PRIORIT	Y APP	LN.	INFO	. :							997-							
									HU	1	998-	2180		- 1	A	199	810	001
											998-							
											998-		14	- 2	A3	199	81:	124
AB Th	e tit	le p	roce	ss c	ompr:	ises	, e.	g., (conden	sa	tion	of						

4-oxiranylmethoxy-9H-carbazole with 2-(MeO)C6H4OCH2CH2NHCH2Ph in a protic organic solvent followed by deprotection.

3246-03-5P ΙT

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation of carvedilol)

RN 3246-03-5 HCAPLUS

Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME) CN

ΤТ 72956-09-3P, Carvedilol 95093-99-5P, (+)-Carvedilol 95094-00-1P, (-)-Carvedilol

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(preparation of carvedilol)

RN

72956-09-3 HCAPLUS
2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-CN (CA INDEX NAME)

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PAGE 2-A

RN 95093-99-5 HCAPLUS

Absolute stereochemistry. Rotation (+).

RN 95094-00-1 HCAPLUS

2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, CN (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

REFERENCE COUNT: THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d 119 ibib abs hitstr tot

L19 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:1154673 HCAPLUS

DOCUMENT NUMBER: 142:93675

TITLE: A process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-

methoxyphenoxy)ethyllaminolpropan-2-ol

INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev; Thennati, Rajamannar

Sun Pharmaceutical Industries Limited, India PATENT ASSIGNEE (S):

SOURCE: PCT Int. Appl., 27 pp. CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

KIND DATE APPLICATION NO. PATENT NO. WO 2004113296 A1 20041229 WO 2004-IN52 20040304 W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG IN 2003MU00647 IN 2003-MU647 20050211 20030620 A1 20061130 US 2006270858 US 2005-553957 20051019 A 20030620 IN 2003-MU647 PRIORITY APPLN. INFO.: A 20030717 W 20040304 IN 2003-MU721 WO 2004-IN52 OTHER SOURCE(S): CASREACT 142:93675; MARPAT 142:93675 GI

- * STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY AVAILABLE VIA OFFLINE PRINT *
- AB The present invention provides a process for preparation of 1-[9H-carbazol-4-yloxy]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I. if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)phenoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnC12, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75° for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NH3. The aqueous layer was separated, and the

product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet % Pd/C catalyst (50% moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature 60-70° for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for .apprx.10 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and

toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

T 72956-09-3P, Carvedilol 95093-99-5P,
(R)-1-(9H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-

ol 95094-00-1P, (S)-1-(9H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-ol

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP

(Preparation) (preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino](CA INDEX NAME)

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PAGE 2-A

RN 95093-99-5 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2R)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

- RN 95094-00-1 HCAPLUS
- CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-, (2S)- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

- IT 51997-51-4, 4-(Oxiranylmethoxy)-9H-carbazole 95093-95-1,
 - (S)-4-(Oxiranylmethoxy)-9H-carbazole 95093-96-2,
 - (R)-4-(Oxiranylmethoxy)-9H-carbazole
 - RL: RCT (Reactant); RACT (Reactant or reagent)

(reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)

- RN 51997-51-4 HCAPLUS
- CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

RN 95093-95-1 HCAPLUS

CN 9H-Carbazole, 4-[(2S)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry.

RN 95093-96-2 HCAPLUS

CN 9H-Carbazole, 4-[(2R)-2-oxiranylmethoxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

REFERENCE COUNT:

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:556143 HCAPLUS

DOCUMENT NUMBER: 137:125080

TITLE: Process for preparing heterocyclic indene

analogs by cyclocarbonylation at moderate temperatures

and catalyst loading

INVENTOR(S): Scalone, Michelangelo; Zeibig, Thomas Albert

PATENT ASSIGNEE(S): Hoffmann-LaRoche Inc., Switz.

SOURCE: U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION:

PATENT NO.						DATE						DATE					
US 2002099223									2002-								
US	6777	559			B2		2004	0817									
CA	CA 2434408				A1	2002	0801		CA :	2002-		20020122					
				A2	A2 20020801 WO 2002-EP583								20020122				
WO	2002	0590	89		A3		2002	1031									
	W:	ΑE,	AG,	AL,	AM,	ΑT,	AU,	ΑZ,	BA,	BB	, BG,	BR,	BY,	ΒZ,	CA,	CH,	CN,
		CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC	, EE,	ES,	FI,	GB,	GD,	GE,	GH,
		GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE	, KG,	KΡ,	KR,	ΚZ,	LC,	LK,	LR,
											, MW,						
							SG,	SI,	SK,	SL	, TJ,	TM,	TR,	TT,	TZ,	UA,	UG,
					ZA,												
	RW:										, TZ,						
											, IT,						
											, GW,						
AU 2002247645								AU 2002-24/645 EP 2002-716673									
EP																	
	R:										, IT,		LU,	NL,	SE,	MC,	PT,
											, TR				_		
JP	2004	5194	65		Т		2004	0702		JP :	2002-	5593	91		2	0020	122
TM	2003	CNOI	126		A		2005	0422		IN :	2003-0	CNII	26		2	0030	722
MA	2003	PAUG	000		A		2003	0922		MA.	2003-1	PAGG	06		2	0030	123
										US .	2004-	1632	96			0040	122
	7169 APP				BZ		2007	0130		PD .	2001-	1016	0.4			0010	100
(11)	I APP	LIN.	INFO	. :													
											2002-1 2002-1						
										WU.	2002-	BE 38	0		vı Z	UU2U	166

OTHER SOURCE(S):

AB A process for the preparation heterocyclic indene analogs, especially with the preparation of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves cyclocarbonylation followed by saponification This process avoids high temps. and high catalyst loadings.

CASREACT 137:125080; MARPAT 137:125080

IT 51997-51-4P, 4-Oxiranylmethoxy-9H-carbazole 72956-09-3P, Carvedilol

RL: IMF (Industrial manufacture); PREP (Preparation)

(process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)

RN 51997-51-4 HCAPLUS

CN 9H-Carbazole, 4-(2-oxiranylmethoxy)- (CA INDEX NAME)

RN

72956-09-3 HCAPLUS 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME) CN

PAGE 1-A

PAGE 2-A

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L20 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2004:1154673 HCAPLUS

DOCUMENT NUMBER: 142:93675

TITLE: A process for preparation of

1-[9H-carbazol-4-yloxy]-3-[[2-(2methoxyphenoxy)ethyl]amino]propan-2-ol

INVENTOR(S): Chhabada, Vijay Chhangamal; Rehani, Rajeev Budhdev;

Thennati, Rajamannar

Sun Pharmaceutical Industries Limited, India PATENT ASSIGNEE(S):

PCT Int. Appl., 27 pp. SOURCE:

CODEN: PIXXD2 DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

GI

PATENT NO.					KIND DATE			APPLICATION NO.						DATE			
WO 20	WO 2004113296				A1 20041229			WO 2004-IN52						20040304			
W	: AE,	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BW,	BY,	BZ,	CA,	CH,	
	CN,	CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	EG,	ES,	FI,	GB,	GD,	
	GE,	GH,	GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KZ,	LC,	
	LK,	LR,	LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN.	MW,	MX,	MZ,	NA,	NI,	
	NO,	NZ,	OM,	PG,	PH,	PL,	PT,	RO,	RU,	SC,	SD,	SE,	SG,	SK,	SL,	SY,	
		TM,															
F	W: BW.	GH.	GM,	KE.	LS,	MW.	MZ,	SD,	SL,	SZ.	TZ.	UG,	ZM,	ZW,	AM,	AZ,	
	BY,	KG,	KZ.	MD.	RU,	TJ.	TM.	AT.	BE.	BG.	CH,	CY.	CZ,	DE.	DK,	EE.	
	ES.	FI,	FR.	GB.	GR.	HU.	IE.	IT.	LU.	MC.	NL.	PL.	PT.	RO.	SE.	SI.	
		TR.															
	TD.	TG															
IN 2003MU00647				A		2005	0211	IN 2003-MU647						2	0030	620	
US 2006270858				A1 20061130 US 2005-553957							20051019						
PRIORITY APPLN. INFO.:				IN 2003-MU647						7							
					IN 2003-MU721							A 20030717					
									WO 2	004-	IN52			W 2	0040	304	
OTHER SOURCE(S):					CASREACT 142:93675; MARPAT 142:93675												

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

The present invention provides a process for preparation of 1-[9H-carbazol-4-vloxv]-3-[[2-(2-methoxyphenoxy)ethyl]amino]-propan-2-ol (I) in racemic form or in the form of optically active R or S enantiomer or its pharmaceutically acceptable salt, comprising, reacting 4-(oxiranylmethoxy)-9H-carbazole (II) or the R or S enantiomer thereof with a compound of formula (III) (wherein R1 = benzyl or substituted benzyl), in an aprotic organic solvent in presence of a catalyst to obtain a compound of formula (IV) (wherein R1 is as defined above), or the R

04/18/2008 Page 110 or S enantiomer thereof. The resultant compound IV is subjected to debenzylation reaction by catalytic hydrogenation to obtain the compound I, if desired converting the resultant compound I to a pharmaceutically acceptable salt thereof. Thus, to 400 mL EtOAc, 70 g (0.27 mol) anhydrous N-[2-[2-(methoxy)]pehnoxy]ethyl]benzylamine, 10.25 g (0.075 mol) anhydrous ZnCl2, and 50 g (0.21 mol) 4-(oxiranylmethoxy)-9H-carbazole were added and the reaction mixture was heated to 70-75 for 3 h (TLC control for checking conversion to N-benzylcarvedilol), cooled to ambient temperature, and quenched into 100 mL 12-15% aqueous NBI3. The aqueous layer was separated, and

the

RN

product enriched organic layer was washed with water till neutral Ph, treated with charcoal, and filtered. To this solution of N-benzyl carvedilol in EtOAc, 7 g wet 5\$ Pd/C catalyst (50\$ moisture content) was added and the reaction mixture was hydrogenated at 3.5-4.5 Kg/cm2 at temperature $60-70^\circ$ for a period of about 10 h and filtered. The filtrate was concentrated to remove EtOAc. To the resultant syrupy mass n-butanol (100 mL) was added and the solution was stirred for appraval0 h. The crystals were separated by filtration, washed successively with n-butanol (50 mL) and toluene (50 mL) to obtain carvedilol (47 g) which was recrystd. from 3 vols. EtOAc to obtain carvedilol (42 g).

IT 72956-09-3P, Carvedilol 95093-99-5P,

(R)-1-(9H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2ol 95094-00-lP, (S)-1-(9H-Carbazol-4-yloxy)-3-[[2-[2-(methoxy)phenoxy]ethyl]amino]propan-2-0

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-(CA INDEX NAME)

PAGE 1-A

PAGE 2-A

RN 95093-99-5 HCAPLUS

Absolute stereochemistry. Rotation (+).

RN 95094-00-1 HCAPLUS

Absolute stereochemistry. Rotation (-).

- - (reactant; preparation of carvedilol by amination of oxiranylmethoxycarbazole with N-(methoxyphenoxyethyl)benzylamine and hydrogenolysis of N-benzylcarvedilol)
- RN 3246-03-5 HCAPLUS
- CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

REFERENCE COUNT:

2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT L20 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:556143 HCAPLUS

DOCUMENT NUMBER: 137:125080

TITLE: Process for preparing heterocyclic indene

analogs by cyclocarbonylation at moderate temperatures and catalyst loading

INVENTOR(S): Scalone, Michelangelo; Zeibig, Thomas Albert

PATENT ASSIGNEE(S): Hoffmann-LaRoche Inc., Switz.

SOURCE: U.S. Pat. Appl. Publ., 19 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION:

PATENT NO.								APPLICATION NO.										
US	US 2002099223				A1 20020725			US 2002-54462										
US	US 6777559			B2 20040817														
								CA 2002-2434408						20020122				
WO	WO 2002059089				A2 20020801				WO :	2002-1		20020122						
WO	0 2002059089				A3 20021031													
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		LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN	, MW,	MX,	MZ,	NO,	NZ,	PH,	PL,	
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		CY,	DE,	DK,	ES,	FI,	FR,	GB,	GR,	ΙE	, IT,	LU,	MC,	NL,	PT,	SE,	TR,	
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AU	AU 2002247645			A1 20020806				AU 2002-247645										
EP				A2 20031029				EP 2002-716673					20020122					
	R:	AT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR	, IT,	LI,	LU,	NL,	SE,	MC,	PT,	
		IE,	SI,	LT,	LV,	FI,	RO,	MK,	CY,	AL	, TR							
JP	2004	5194	65		T		2004	0702		JP :	2002-	5593	91		2	0020	122	
IN	IN 2003CN01126			A 20050422				IN 2003-CN1126					20030722					
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US	2004	1277	23		A1		2004	0701		US :	2004-	7632	96		2	0040	122	
US	7169	935			B2		2007	0130										
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										US :	2002-	5446	2	- 1	A3 2	0020	122	
										WO :	2002-1	EP58	3	1	7 2	0020	122	

OTHER SOURCE(S): CASREACT 137:125080; MARPAT 137:125080

AB A process for the preparation heterocyclic indene analogs, especially with the preparation of 4-hydroxycarbazole or N-protected 4-hydroxycarbazole, involves cyclocarbonylation followed by saponification This process avoids high temps, and high catalyst loadings.

IT 72956-09-3P, Carvedilol

RL: IMF (Industrial manufacture); PREP (Preparation) (process for preparing heterocyclic indene analogs by

cyclocarbonylation at moderate temps. and catalyst loading)

RN 72956-09-3 HCAPLUS

CN 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino](CA INDEX NAME)

PAGE 1-A

PAGE 2-A

MeO

IT 3246-03-5

RL: RCT (Reactant); RACT (Reactant or reagent) (process for preparing heterocyclic indene analogs by cyclocarbonylation at moderate temps. and catalyst loading)

RN 3246-03-5 HCAPLUS

CN Benzenemethanamine, N-[2-(2-methoxyphenoxy)ethyl]- (CA INDEX NAME)

REFERENCE COUNT:

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> log y COST IN U.S. DOLLARS

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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL
CA SUBSCRIBER PRICE	-29.60	-29.60

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